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CONTENTS OF VOLUME XVIII

JULY, 1916. NUMBER 1

PAGE

Introduction to the Third Report of the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital. J. F. Siler, M.D., P. E. Garrison, M.D., and W. J. MacNeal, M.D., New York 1

The Hereditary Factor in Pellagra. C. B. Davenport, Ph.D., Cold Spring Harbor, Long Island, N. Y. 4

A Study of the Heredity of Pellagra in Spartanburg County, South Carolina. Elizabeth B. Muncey, M.D., Cold Spring Harbor, Long Island, N. Y. 32

Studies in Cerebral Fat Embolism. With Reference to the Pathology of Delirium and Coma. Harry Gauss, M.D., Chicago 76

A Critical Consideration of Systemic Blastomycosis. With Notes on Certain Special Features and Report of Five Cases. H. Windsor Wade, M.D., and George S. Bel, M.D., New Orleans 103

Metabolism Studies Before and After Splenectomy in a Case of Pernicious Anemia. O. H. Perry Pepper, M.D., and J. Harold Austin, M.D., Philadelphia 131

Book Review: Modern Medicine. Its Theory and Practice. In Original Contributions by American and Foreign Authors. Edited by Sir William Osler, Bart., M.D., F.R.S. 136

AUGUST, 1916. NUMBER 2

PAGE

Dietary Deficiency as the Etiological Factor in Pellagra. Edward B. Vedder, M.D., Washington, D. C. 137

The Incidence of Pellagra in Spartanburg County, S. C., and the Relation of the Initial Attack to Race, Sex and Age. J. F. Siler, M.D., P. E. Garrison, M.D., and W. J. MacNeal, M.D., New York .. 173

The Lime Deficiency of Diabetes. Max Kahn, M.D., Ph.D., and Morris H. Kahn, M.D. 212

Further Studies in the Inactivation of Pepsin. The Effect of Various Salts and Alkaline Substances. Walter W. Hamburger, M.D., and Benjamin Halpern, M.D., Chicago 228

The Rate of Absorption of Various Digitalis Preparations from the Gastro-Intestinal Tract. Charles C. Haskell, C. S. McCants and F. P. Gardner, Richmond, Va. 235

Ventricular Escape with Observations on Cases Showing a Ventricular Rate Greater Than That of the Auricles. Paul D. White, M.D., Boston 244

A Study of Proteins in Urine, and a Comparison of Gravimetric and Nephelometric Methods for Their Estimation. J. T. W. Marshall, H. W. Banks, Jr. and S. S. Graves 250

Transient Auricular Fibrillation. An Electrocardiographic Study. Edward B. Krumbhaar, M.D., Philadelphia 263

SEPTEMBER, 1916. NUMBER 3

PAGE

Dissociated Jaundice. C. F. Hoover, M.D., and M. A. Blankenhorn, M.D., Cleveland 289

A Comparison, in Various Diseases, of the Carbon Dioxid Tension in the Alveolar Air (Plesch Method) with the Amount of Carbon Dioxid in the Venous Blood (Van Slyke's Method). I. Chandler Walker, M.D., and Channing Frothingham, Jr., M.D., Boston ... 304

Chronic Influenza in Pulmonary Tuberculosis. Mary L. Hamblet, M.D., and Harry Lee Barnes, M.D., Wallum Lake, R. I. 313

Studies in Blood Pressure. With Especial Reference to Diastolic and Pulse Pressure Readings. William W. Cadbury, M.D., Boston 317

The Subsequent History of Pellagrins in Spartanburg County, S. C., Who Survived the Initial Attack. J. F. Siler, M.D., P. E. Garrison, M.D., and W. J. MacNeal, M.D., New York 340

The Treatment of Syphilis of the Central Nervous System. With Intravenous Salvarsan Alone, with Intravenous Salvarsan and Intraspinal Salvarsanized Serum Together and with Intraspinal Salvarsanized Serum Alone. I. C. Walker, M.D., and D. A. Haller, M.D., Boston 376

A Note on the Blood Fat Before and After Splenectomy. Harry Dubin, Ph.D., and Richard M. Pearce, M.D., Philadelphia 426

Book Review:

The Physiology of the Amino-Acids. Frank P. Underhill, Ph.D. [illegible]

The Archives of Internal Medicine

Vol. XVIII DECEMBER, 1916. No. 6

ACIDOSIS IN ACUTE AND CHRONIC DISEASE*

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BOSTON

The term acidosis as it is used in medicine at the present time does not designate a definite clinical entity, but is applied to a variety of conditions in which, as Sellards[1] expresses it, there is a general impoverishment of the body in bases or substances which readily give rise to bases. This impoverishment in bases may be due to faulty absorption of bases, to an unusual loss of them from the body, or to their neutralization by abnormal amounts of acids. Increase in the amounts of acids in the body may be due to the production of abnormal acids, an overproduction of the usual body acids, or, as Howland and Marriott[2] have recently suggested, to an accumulation of normal acids due to failure in excretion.

It is difficult, if not impossible, at the present time to estimate what are the normal amounts of bases and acids in the body. Probably considerable variation occurs under different physiologic conditions. Y. Henderson recently emphasized the variations due to changes in elevation above sea level that occur in healthy subjects in some of the tests for so-called acidosis.

The methods used in testing for evidence of so-called acidosis are numerous. They consist in a direct examination of the blood, a study of the urine, a study of the products of respiration, and an estimation of the amount of alkali necessary to render the urine alkaline when administered by mouth or intravenously.

In the direct examination of the blood for evidence of so-called acidosis many studies have been made of the carbon dioxid content of the blood. It has been known for a long time that this acid diminishes in amount in the blood as other acids increase, except when variations in the excitability of the respiratory center occur, as Hasselbalch[3] and others have pointed out. A diminution of the carbon dioxid

* Submitted for publication July 11, 1916.

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1. Sellards: Bull. Johns Hopkins Hosp., 1914, xxv, 101.
2. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, xxvii, 63.
3. Hasselbalch: Biochem. Ztschr., 1912, xlvi, 403.

in the blood, therefore, has been looked on as evidence of acidosis. Pflüger,[4] Senator,[5] Geppert,[6] and Minkowski[7] were conspicuous among the early workers on the subject of diminished carbon dioxid in the blood in fevers. Their work, which was carried out on animals under different experimental conditions, consisted in direct examination of either the venous or the arterial blood. The lowering of the carbon dioxid content in the blood which they found in fevers was considered to be due to an increase in other acid substances. In 1889 Kraus,[8] applying this test to man, found that the amount of carbon dioxid in the blood was diminished in fevers. He studied a few cases of typhoid fever, tuberculosis, erysipelas, scarlatina, pneumonia, and acute articular rheumatism. In 1912 Peabody[9] studied the carbon dioxid content of the blood in pneumonia and found it usually low, occasionally normal, and rarely above normal. In the severer cases and terminal stages of the disease the carbon dioxid was usually low. Van Slyke[10] has recently devised a relatively simple method for estimating the amount of carbon dioxid in the blood. This method should be of great assistance in detecting acidosis.

Studies on the hydrogen ion concentration of the blood for evidence of acidosis have been made by Peabody[11] in chronic nephritis and cardiac cases. He found the hydrogen ion concentration of the blood remained quite constant in his cases. Rolly[12] has made an extensive study of the hydrogen and hydroxyl ions in the blood in a variety of diseases and concludes from his observations that the alkalinity of the blood is lowered in diabetes, nephritis, severe anemia, and the gastrointestinal diseases of childhood, while, on the other hand, in diseases of the liver and in exophthalmic goiter the alkalinity of the blood is increased.

In 1888 von Jaksch[13] reported a diminished alkalinity of the blood in uremia, fever, destructive liver disease, leukemia, chlorosis, primary anemia and carbon monoxid gas poisoning. In 1914 Sellards[1] estimated the titratable alkalinity of the blood in various conditions in which acidosis is present as shown by other tests, and found it diminished. He also found it lowered in certain chronic nephropathies and in some anemias.

4. Pflüger: Arch. f. d. ges. Physiol., 1868, i, 297.
5. Senator: Untersuchungen über fieberhaften Process und seine Behandlung, Berlin, 1873, p. 74.
6. Geppert: Ztschr. f. klin. Med., 1881, ii, 355.
7. Minkowski: Arch. f. exper. path. u. Pharmakol., 1885, xix, 209.
8. Kraus: Ztschr. f. Heilk., 1889, x, 106.
9. Peabody: Jour. Exper. Med., 1912, xvi, 701.
10. Van Slyke: To be published in the Jour. Biol. Chem.
11. Peabody: The Archives Int. Med., 1914, xiv, 236.
12. Rolly: München. med. Wchnschr., 1912, lix, 1201.
13. Von Jaksch: Ztschr. f. klin. Med., 1888, xiii, 350.

In 1913 Marriott[14] reported a method for estimating the amount of oxybutyric acid in a small amount of blood collected from a vein, and in 1914[15] showed that although traces of this acid might be present in the blood during health it was increased ten to twenty fold in the acidosis of diabetes. Recently Howland and Marriott[16] have reported that different acid substances, especially the acid phosphates, are increased in amount in the blood of patients with chronic nephritis.

It is to be expected that further studies on human blood will reveal cases in which normal acids are increased in amount in the blood in different diseases, or in which acids are present which are not present under normal conditions.

In considering the methods advocated for detecting the presence of acidosis by examination of the urine no attempt will be made completely to review the subject. Attention will simply be called to certain of the tests which have been used considerably of late by investigators. It must be remembered that just criticism has been raised against most of these urinary tests for acidosis, because they simply show what is excreted, and not what remains in the body. Careful studies have shown that frequently the body is unable to excrete in the urine those substances which have been looked on as indicative of acidosis.

Since Stadelmann[17] discovered oxybutyric acid in the urine of diabetics in 1883, the presence of this substance or diacetic acid or acetone in the urine has been looked on as an indication of acidosis. At one time the amounts of these substances in the urine were used as indications of the degree of acidosis, but it has now been shown definitely that considerable amounts of oxybutyric acid may be present in the blood with only traces of acetone in the urine. On the other hand, there seems to be always some trace of acetone in the urine when there is much oxybutyric acid in the blood. Von Noorden[18] mentions in his book that acetone has been found in scarlatina, measles, typhoid and severe dysentery. Howland and Marriott[2] consider that it occurs in most of the infectious diseases of childhood, just as fever occurs. In addition to the above, Taylor[19] found acetone in the urine in eclampsia and phosphorus poisoning. It is also well known that acetone bodies occur in the urine in starvation and after anesthesia. Therefore acetone in the urine may be looked on as an indication that abnormal acids

14. Marriott: Jour. Biol. Chem., 1913, xvi, 293.
15. Marriott: Jour. Biol. Chem., 1914, xviii, 507.
16. Howland and Marriott: Reported at meeting of the American Society for the Advancement of Clinical Investigation, 1916.
17. Stadelmann: Arch. f. exper. Pathol. u. Pharmakol., 1883, xvii, 419.
18. Von Noorden: Metabolism and Practical Medicine, Chicago Medical Book Co., 1907, ii, 160.
19. Taylor: Digestion and Metabolism, Lea & Febiger, Philadelphia, 1912, p. 362.

are present in the blood, but it is no indication of how large a quantity of them are present.

The relation of the amount of ammonia to the total nitrogen in the urine has been studied as an indication of excessive production of acid substances in the body. An increase in the relative amount of ammonia is looked on as an indication of so-called acidosis, although it must be borne in mind that certain diets rich in protein and diseases which cause a large breaking down of protein may show a relative as well as actual increase in ammonia nitrogen in the urine. Boussingault's[20] observation in 1850 that the ammonia in diabetic urines was increased was brought to the attention of medical men again in 1880 by Hallervorden.[21] Since that time many observers have confirmed this fact and used it as a means of determining the degree of acidosis, especially in diabetes. Sellards[22] has found the ammonia in the urine increased in Asiatic cholera. Pfaundler[23] reports it increased in diseases of the liver and in gastro-intestinal disorders of children. Palmer and Henderson[24] feel that the increase in ammonia in the urine indicates the degree of acidosis only in those cases in which the acidosis is due to the formation of oxybutyric acid. Howland and Marriott[2] perhaps sum up the question of the relation between a relative increase in the ammonia in the urine and acidosis by saying that such an increase suggests an acidosis, but needs confirmation by other tests.

In recent years studies have been made on the hydrogen ion concentration of the urine as estimated by Henderson's method. Henderson and Palmer[25] found that in certain diseases the average hydrogen ion concentration was lower than in healthy persons, but the individual variations in the different groups make the test unreliable.

Since Haldane and Priestley[26] in 1905 devised a relatively simple method for determining the amount of carbon dioxid in the alveolar air, this test has been much used for studies on acidosis. It is well known that the alveolar carbon dioxid corresponds closely to that in the arterial blood, and that as other acids increase this acid diminishes in amount in the blood. Thus a reduction of the tension of the carbon dioxid in the alveoli is looked on as an indication of acidosis, unless changes in the irritability of the respiratory center are present.

Von Rubow[27] and Beddard and Pembrey[28] in 1908 found a lowered

20. Boussingault: Jour. f. prakt. Chem., 1850, li, 281.
21. Hallervorden: Arch. f. exper. Path. u. Pharmakol., 1879-1880, xii, 237.
22. Sellards and Shaklee: Philippine Jour. Sc., 1911, vi, 53.
23. Pfaundler: Jahrb. f. Kinderh., 1904, lx, 719; ibid., 1901, liv, 247.
24. Palmer and Henderson: THE ARCHIVES INT. MED., 1913, xii, 153.
25. Henderson and Palmer: Jour. Biol. Chem., 1913, xii, 393.
26. Haldane and Priestley: Jour. Physiol., 1905, xxxii, 225.
27. Von Rubow: Festschr. b. d. Einweihung der Finseninst Klinik für innere Krankh., 1908, p. 26.
28. Beddard and Pembrey: Brit. Med. Jour., 1908, ii, 580.

carbon dioxid tension in the alveolar air in cardiac cases which showed cyanosis. Fitzgerald[29] also found the carbon dioxid tension in the alveolar air below normal in cases of congenital heart disease. Beddard and Pembrey[25] found evidence of acidosis by this test in diabetes. Porges, Leimdörfer and Markovici[30] confirmed this finding and found also that the carbon dioxid tension was lowered in cardiac dyspnea. Friderica and Olsen[31] report evidence of acidosis as shown by this test in some cases of erysipelas, mumps and angina, but not uniformly. Straub and Schlayer[32] in 1912 found the carbon dioxid tension diminished in the alveolar air in cases of chronic nephritis. Evidence of acidosis in certain cases of chronic nephritis as shown by this test has also been found by Peabody,[33] Porges and Leimdörfer[34] and others. Roth[35] reports evidence of diminished carbon dioxid tension in the alveolar air in cases of obesity and in certain surgical cases.

The estimation of the degree of acidosis by determining the amount of sodium bicarbonate taken by mouth or intravenously which is necessary to render the urine alkaline has been used extensively by Sellards. He[26] found increased tolerance to sodium bicarbonate in some of the nephropathies, Asiatic cholera, some anemias, rheumatic fever and diabetes. Palmer and Henderson[24] in 1913 applied the principle of this test in a somewhat different form and found evidence of acidosis in nephritis. Peabody[37] has also found evidence of acidosis by the so-called soda tolerance test of Sellards in nephritis.

It is evident from this short review that signs of so-called acidosis, as detected by various tests, may exist in numerous diseases. In each disease, however, all the tests may not be positive, as for example acetone may be found in diabetes and in diseases in children, while in chronic nephritis it is not present; yet all of these conditions may show the alveolar carbon dioxid lowered or the sodium bicarbonate tolerance increased. It would seem, therefore, that so-called acidosis is not due in each case to the same abnormal factors.

It has been the object of this work to study on the same case at the same time several of these tests for so-called acidosis with a view of finding out how the cases in which an acidosis is supposed to exist react to the different tests. Also, it was thought that evidence of

29. Fitzgerald: Jour. Path. and Bact., 1909-1910, xiv, 328.
30. Porges, Leimdörfer and Markovici: Ztschr. f. klin. Med., 1911, lxxiii, 389.
31. Friderica and Olsen: Deutsch. Arch. f. klin. Med., 1912, cvii, 236.
32. Straub and Schlayer: München. med. Wchnschr., 1912, lix, 569.
33. Peabody: The Archives Int. Med., 1914, xiv, 236.
34. Porges and Leimdörfer: Ztschr. f. klin. Med., 1913, lxxvii, 464.
35. Roth: Jour. Am. Med. Assn., 1915, lxv, 413.
36. Sellards: Bull. Johns Hopkins Hosp., 1914, xxv, 141.
37. Peabody: The Archives Int. Med., 1915, xvi, 955.

acidosis might appear in certain diseases in which its presence has not as yet been expected.

For this purpose cases were selected from the wards of the Peter Bent Brigham Hospital for study. So far as possible cases were chosen which presented an uncomplicated picture of a single disease. In each case the carbon dioxid tension in the alveolar air was determined, the soda tolerance test was carried out, and the twenty-four-hour specimen of urine was examined for the presence of acetone, for its hydrogen ion concentration, for the total nitrogen and for the ammonia nitrogen.

The Plesch[38] method as modified by Higgins[39] was used for collecting the alveolar air, which was then examined by the method devised by Haldane[40] for gas analysis. That this method is satisfactory even in cases in which the patient is breathing rapidly or is unable to cooperate with the investigator has been shown by Walker and Frothingham.[41] We (Walker and Frothingham) compared the results obtained by this method with the results obtained by examination of the venous blood direct, as recommended by Van Slyke, and found that they agreed very well in most cases. With this method under these conditions it seems fair to call the carbon dioxid tension normal when it falls between 39 and 45 mm. The alveolar air in each case was collected for examination at some time during the twenty-four hours in which the urine was collected or just after the twenty-four hours were up on the following morning before the soda tolerance test was started. Most of the samples of alveolar air were collected about two or three hours after a meal.

In studying the amount of sodium bicarbonate necessary to make the urine alkaline to litmus, 5 gm. at a time were given by mouth. At the end of two hours the patient voided the urine and if it was still acid the dose was repeated. If the patient was unable to void the next dose was put off until after the next urination. If the test was carried on through the night the patients were not aroused, so the intervals became longer. It usually takes from 5 to 15 gm. of sodium bicarbonate to change the reaction of a healthy person's urine from acid to alkaline. In a few cases the urine became amphoteric, in which cases the test was continued until it became definitely alkaline to litmus. This test was performed on the morning after the twenty-four-hour urine had been collected.

In the twenty-four-hour urines a small amount of toluol was used

38. Plesch: Ztschr. f. exper. Path. u. Therap., 1909, iii, 380.
39. Higgins: Publication No. 203, Carnegie Inst. of Washington, 1915, p. 168.
40. Haldane: Methods of Air Analysis, London, Charles Griffin & Co., Ltd., 1912.
41. Walker and Frothingham: Tr. Am. Soc. for the Advancement of Clinical Investigation, 1916. Now published in THE ARCHIVES INT. MED., September, 1916.

as a preservative. In some cases, due to contamination with feces or to errors on the part of those collecting the urines, the full twenty-four-hour amount was not obtained, but it was felt that probably these losses made little difference in the relation of ammonia to the total nitrogen.

The ammonia is recorded as ammonia nitrogen. This and the total nitrogen of the urine were estimated by Folin's[42] method. The ammonia nitrogen is usually estimated under normal conditions at from 2 to 7 per cent. of the total nitrogen.

The hydrogen ion concentration of the urine was determined by Henderson's method and recorded as the logarithm with the minus sign omitted. Henderson and Palmer[25] found the average of 100 healthy cases to be P_H^+ 6.3. The presence of acetone was looked for by shaking the urine with glacial acetic acid and sodium nitroprussid and then adding ammonia. No attempt was made to determine quantitatively this substance.

The results of these studies are presented in the form of tables. Cases of the same disease are grouped together in one table and a few words of explanation are added to emphasize the interesting points. The actual date of the observation and the medical number of the patient are recorded so that by reference to the hospital records the exact condition of the patient at the time of the tests may be ascertained.

TABLE 1.—SYPHILIS

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2 per Cent.	P_H^+	Acetone	
11/ 5/15	3540	42	2.9	7.3	0	5
1/ 6/16	3857	44.2	2.8	5.9	0	10
2/17/16	4143	43.2	5.5	5.8	0	5

In Table 1 are grouped three cases of syphilis which showed evidence of a generalized infection with the spirochetes. It will be readily seen that in each case all the tests fall within normal limits and therefore no suggestion of acidosis is present.

In Table 2 are included two patients with epilepsy on whom the tests were taken between attacks, which came in only infrequent intervals. In these cases there is no evidence of acidosis in any of the tests used.

42. Folin and McCallum: Jour. Biol. Chem., 1912, xi, 523. Folin and Farmer: Ibid., 493.

Six cases of diabetes are presented in Table 3. In five of these cases it will be seen that there is evidence of acidosis and, furthermore, that each of these five cases shows variations from the normal in all of the tests used except in the hydrogen ion concentration of the urine. As will be observed in the other groups, this test shows such marked variation in the individual cases that it does not seem to be reliable as

TABLE 2.—EPILEPSY

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2 - N_2 per Cent.	P_H^+	Acetone	
11/ 3/15	3517	42.7	5.0	5.6	0	10
11/ 3/15	3514	39.1	6.3	5.8	0	10

a guide to acidosis. The remaining case was a mild case and showed no evidence of acidosis by any of the tests. If we assume that the acidosis of diabetes is due entirely to the presence of increased amounts of oxybutyric acid, we may expect that acidosis due to this cause in other diseases will give positive results with all these tests except the hydrogen ion concentration of the urine. Of course other factors than oxybutyric acid may take part in the acidosis of diabetes.

TABLE 3.—DIABETES

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2 - N_2 per Cent.	P_H^+	Acetone	
12/14/15	3738	34.7	18.2	6.2	+	35
12/15/15	3746	36.6	11.2	5.1	+	45
12/15/15	3757	34.6	18.9	below 4.7	+	65
1/ 4/16	3880	32.3	20.4	5.9	+	60 amphoteric 90 total
1/24/16	4008	40.8	4.6	5	0	10
1/25/16	3988	35.5	10.3	5.5	+	55

Quite a different condition from the acidosis in diabetes is seen in the nine cases of exophthalmic goiter in Table 4. These cases represent various degrees of activity of the disease. In some of these cases the carbon dioxid tension in the alveolar air was quite high. Acetone was never present and the urine became alkaline on small amounts of sodium bicarbonate in four of the cases. The percentage of ammonia nitrogen to total nitrogen varied considerably, but in no case did it

reach 10 per cent. The hydrogen ion concentration shows variations from one end of the scale used to the other.

Eight cases of primary anemia with quite marked blood changes are shown in Table 5. Evidence of acidosis is suggested in the alveolar air and soda tolerance tests in two cases, but both of these

TABLE 4.—EXOPHTHALMIC GOITER

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2– N_2 per Cent.	P_H^+	Acetone	
11/ 4/15	3434	54.4	2.8	7.3	0	15
11/16/15	3591	47.2	2.8	6.3	0	10 amphoteric 15 total
12/16/15	3792	43.5	6.9	6.4	0	10
12/16/15	3748	45.4	7.0	5.8	0	10
1/13/16	3896	47.7	2.1	4.7	0	5
1/21/16	3989	41.2	7.6	5.9	0	0
1/27/16	4040	40.9	4	7	0	5
2/ 1/16	4075	40.6	6.4	6.2	0	5
3/17/16	4311	43.9	7.8	below 4.7	0	10 amphoteric 15 total

TABLE 5.—PRIMARY ANEMIA

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2– N_2 per Cent.	P_H^+	Acetone	
10/23/15	3139	40.2	6.9	5.3	0	20
10/26/15	3435	41.2	4	6.6	0	10
11/ 9/15	3538	39.7	5.8	5.2	0	10
11/29/15	3690	39.3	5.5	5.6	0	15 amphoteric 20 total
1/12/16	3863	36.7	7.5	5.6	0	35 taking 1 c.c. dilute HCl t.i.d.
2/ 4/16	4063	42.5	6.9	6.3	0	15
2/29/16	4064	38.6	4	5.2	0	20 taking 1 c.c. dilute HCl t.i.d.
2/29/16	4223	46.2	5.3	5.4	0	10

patients were receiving 1 c.c. of dilute hydrochloric acid three times a day. In other cases the amount of sodium bicarbonate necessary to render the urine alkaline was slightly elevated. The study of the ammonia-nitrogen ratio and the hydrogen ion concentration showed nothing remarkable. Certainly no appreciable degree of acidosis exists in this condition which is detectable by these tests.

Four of the six cases of advanced chronic nephritis in Table 6

show evidence of acidosis by the alveolar air test and the soda tolerance test. The percentage of ammonia is low in most of the cases, which agrees with observations of other workers. Whether this is due to faulty elimination or to the fact that ammonia is not used by the body to make up the deficiency in base met with in chronic nephritis is not clear. As there is no acetone in the urine it is evident that this acidosis is due to some other factor than that which is present in diabetes. The hydrogen ion concentration is fairly constant in these cases and somewhat lowered. Several other cases, not included in the table because all five of the tests could not be completed, showed a very marked reduction in the alveolar air carbon dioxid tension. In one case it was as low as 19 mm.

TABLE 6.—CHRONIC NEPHRITIS

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2 per Cent.	$P_H{}^+$	Acetone	
11/ 5/15	2507	44	6.5	6.2	0	10
11/ 8/15	3360	38.7	1	4.8	0	25+
11/ 8/15	3309	40.1	2.2	5.1	0	50
11/22/15	2307	37.3	4.3	5.1	0	10
1/21/16	3900	39.5	4.2	5.8	0	25
3/ 4/16	4253	29.9	2.8	5.5	0	40+

Twenty-one observations on fifteen cases of pneumonia are recorded in Table 7. In those cases in which two observations were made the second one was after the crisis. Several of these pneumonias terminated fatally. Although the respirations in many of these cases were elevated the results of the carbon dioxid tension determinations in the alveolar air checked up well with the estimation of carbon dioxid in the venous blood. Some of these cases during the course of the disease showed evidence of acidosis by this alveolar air test, while others showed just the reverse. This fits in with Peabody's observation on the blood in pneumonia. He found the carbon dioxid low in some, normal in some and elevated in a few. In a few of the cases the ammonia fraction of the total nitrogen in the urine was elevated appreciably above normal. The hydrogen ion concentration of the urine was quite variable, but on the whole tended to be toward the acid end of the scale. In one case acetone was present. In most of the cases during the height of the fever the amount of sodium bicarbonate necessary to render the urine alkaline was considerably increased. In the cases in which a plus sign is put after the number of grams it signifies that the sodium bicarbonate was discontinued for some

reason before the urine became alkaline. This test certainly suggests that an acidosis is present during the course of the fever in some of these cases. An interesting feature in this group is the fact that the different tests for acidosis show more variable results than in other diseases with acidosis. It suggests, therefore, that if an acidosis is present in pneumonia, it may be due to some other factors besides those that produce the acidosis in diabetes or chronic nephritis.

TABLE 7.—PNEUMONIA

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2 Per Cent.	P_H^+	Acetone	
11/13/15	3608	37.9	26.5	5.5	+	10
11/23/15	3608	39.7	8.3	6.2	0	5 convalescent
11/18/15	3630	40.3	5.6	5.4	0	55
11/23/15	3630	33.8	2.5	6.4	0	10 crisis passed, beginning empyema
11/19/15	3642	34.5	12.3	5.7	0	35+ discontinued
11/26/15	3677	44.2	7.6	5.1	0	40
11/29/15	3690	45.9	9.8	5.3	0	15
12/ 7/15	3690	47.6	7.7	6.1	0	15 convalescent
12/ 8/15	3744	40.6	8.1	5.2	0	35+ discontinued
12/31/15	3883	34.2	7.1	...	0	110
1/10/16	3883	44.7	3.3	5.6	0	15 convalescent
12/31/15	3882	34.7	5	...	0	30
1/10/16	3882	41.9	2.9	6	0	5 convalescent
1/ 4/16	3885	42	5.6	5.4	0	25
1/14/16	3944	38.1	10.7	6.2	0	20 amphoteric 35 total
1/19/16	3965	41.6	5.6	5.2	0	20 brochopneumonia?
1/27/16	4046	45.1	7.5	5.1	0	25
2/ 5/16	4046	45.1	6	5.4	0	15 convalescent
3/17/16	4208	36.3	11.8	5.2	0	5 Crisis on day before tolerance test was done
3/ 7/16	4280	43.1	3.3	4.9	0	15
3/17/16	4237	38.8	9.7	4.7	0	20

In Table 8 are ten observations made on eight cases of acute articular rheumatism. These patients were taking sodium salicylate at the time of the observations. In several of the cases evidence of acidosis was shown by the alveolar air studies, but not in all of them. In one case acetone was present and in another the ammonia was elevated to nearly 10 per cent., but in the other cases these tests showed no evidence of acidosis. Four of the cases showed an increase in the soda

tolerance test. The hydrogen ion concentration of the urine showed too marked variation to be of value in forming an opinion in this disease. It seems fair to say that some form of acidosis occurs in certain of these cases of acute rheumatism, which shows up in one or the other of these tests, but not consistently in any one.

TABLE 8.—Acute Articular Rheumatism

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2–N_2 per Cent.	P_H^+	Acetone	
12/ 2/15	3715	33.2	5.1	5.7	0	10
12/ 7/15	3715	41	2.6	4.9	0	10 convalescent
12/ 2/15	3712	37.1	6.5	5.4	+	15
12/ 3/15	3662	35	5.1	7.1	0	20
12/ 8/15	3662	31.2	4.2	5.1	0	10
2/ 3/16	4088	33.2	6.4	5.3	0	20
3/23/16	4371	38.2	7.6	Below 4.7	0	40
3/27/16	4396	33.1	5.8	7.2	0	10
3/29/16	4417	44.5	6.4	5.6	0	20
4/21/16	4534	42.3	9.8	4.9	0	15

TABLE 9.—Subacute Nephritis

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2–N_2 per Cent.	P_H^+	Acetone	
2/ 2/16	4160	39.5	7.1	6	0	10
3/22/16	4245	46.2	3.6	4.9	0	15
3/22/16	4314	48.5	2.9	5.2	0	10

TABLE 10.—Lung Abscess

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2–N_2 per Cent.	P_H^+	Acetone	
1/12/16	3834	40.4	3.2	5.6	0	15
3/ 7/16	4296	41.2	8.2	5.2	0	10

Three cases of subacute nephritis of a mild grade are presented in Table 9 and show no evidence of acidosis by any of the tests. In two the carbon dioxid tension in the alveolar air was rather high.

Two cases of lung abscess shown in Table 10 also give no evidence of acidosis.

In two cases of gastric cancer (Table 11) the amount of sodium bicarbonate necessary to render the urine alkaline was increased above normal in both. This may possibly have been due to some disturbance in absorption rather than an acidosis. Of the other tests the alveolar air suggested acidosis in one case. The ammonia was high in this case also. The hydrogen ion concentration in the urine represented the two extremes of the scale.

TABLE 11.—GASTRIC CANCER

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2- N_2 per Cent.	P_H+	Acetone	
3/20/16	4236	29.2	7.2	Below 4.7	0	30 amphoteric 45 total
3/23/16	3799	37.4	12.8	7.1	0	5 amphoteric 35 total

TABLE 12.—ADDISON'S DISEASE

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2- N_2 per Cent.	P_H+	Acetone	
10/29/15	3321	28.2	8.2	Below 4.7	0	35
3/11/16	4290	38.7	2.4	Below 4.7	0	15

TABLE 13.—CIRRHOSIS OF THE LIVER

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2- N_2 per Cent.	P_H+	Acetone	
2/ 2/16	4007	42.7	11.5	5.8	0	10
2/18/16	4170	38.2	6	5.1	0	25 (ascites)

In two cases of Addison's disease (Table 12) the carbon dioxid tension was just below the lower limit of normal. In one case the soda tolerance test showed an increase. It is interesting to note that in both the cases the hydrogen ion concentration was more acid than a P_H+ of 4.7, but conclusions from these two cases are hardly justifiable.

In one of the cases of cirrhosis of the liver (Table 13) the ammonia was elevated, as has been noted in diseases of the liver. In the

patient who had ascites the soda tolerance test was increased. This has been the finding in other of our cases of ascites from portal obstruction and probably has some relation to the portal obstruction rather than to an acidosis.

In Table 14 are grouped six cases of chronic cardiac disease. In these cases compensation was fairly well established as long as the patients were quiet in bed. Most of them preferred to have the head somewhat elevated. Except for a diminished carbon dioxid tension in one case and a slightly increased percentage of ammonia in another, there is no evidence of acidosis. In both these cases the other signs of an acidosis were absent. The hydrogen ion concentration of the urine showed such marked variation that no conclusions could be drawn from it.

TABLE 14.—CHRONIC CARDIAC

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH_3/N_2 per Cent.	$P_H{}^+$	Acetone	
11/ 9/15	3562	34.6	2.7	6.4	0	5
11/10/15	3589	46.4	2.8	5.4	0	10
11/17/15	3622	29.1	4.8	7.4	0	5
12/28/15	3730	43.2	6.4	4.7	0	10
12/30/15	3460	40.2	11.7	4.7	0	10
1/31/16	4096	46.3	4.7	5.8	0	5

In Table 10 are grouped seventeen cases representing as many different conditions. In several of them interesting responses to the different tests are seen. In some of them quite marked evidence of acidosis occurs. Acetone was not found in any of these cases, so the type of acidosis was probably different from that found in diabetes. In the cases with an acute infection involving the kidney, in the case of probable miliary tuberculosis and in the case of typhoid fever evidence of acidosis was shown by the alveolar air study and the soda tolerance test. In two of these cases the hydrogen ion concentration of the urine showed it to be strongly acid. One case of gout was interesting, in that it showed no evidence of acidosis. The case of portal thrombosis was of interest in that it showed a high percentage of ammonia nitrogen in the urine, as is reported in liver disorders and a high sodium bicarbonate tolerance, which is probably due to the portal obstruction rather than to an acidosis. The cases of lymphatic leukemia, portal thrombosis and myxedema show a very slight reduction in the carbon dioxid tension of the alveolar air, but too slight to make one feel that any appreciable acidosis exists. The case which

suggested typhus was interesting in that the sodium bicarbonate tolerance was increased, suggesting an acidosis, while the carbon dioxid tension in the alveolar air was high, suggesting just the reverse.

From these studies it seems fair to conclude that the study of the hydrogen ion concentration in the urine is not reliable as an index of acidosis, and therefore it will not be considered further in this summary. It is also clear from this study that evidence of acidosis appears at times in certain diseases, while in other diseases no evidence of it is found. Those diseases which showed an acidosis at times by some

TABLE 15.—MISCELLANEOUS CASES

Date	Med. No.	Alveolar Air CO_2 Tension, Mm.	24-Hour Urine			Sodium Bicarb., Gm.	Diagnosis
			NH_3/N_2 per Cent.	P_H^+	Acetone		
12/21/15	3780	27.4	7.6	Below 4.7	0	80+	Acute infection involving kidney
10/29/15	3423	41.6	3.1	5.6	0	15	Chronic arthritis
10/27/15	3522	36.4	7.9	6.1	0	20	Typhoid fever
10/29/15	3457	28.7	2.6	Below 4.7	0	30	Probably miliary tuberculosis
11/ 3/15	3559	42.2	4.6	5.6	0	20	Tumor in right kidney region
11/10/15	3480	42.5	9.8	5.8	0	15	Fever, mild, unknown cause
11/12/15	3506	41.7	7.8	7.3	0	10	Acute endocarditis
12/14/15	3787	41.9	5.2	5.0	0	10	Acute bronchitis
3/24/16	4359	46.7	6.4	6.4	0	10	Polycythemia
1/ 6/16	3906	39.9	7.1	5.3	0	15	Gonorrheal arthritis
1/12/16	3955	41.9	6.1	5.6	0	15	Perirenal abscess
1/24/16	4025	45.9	7.5	5.4	0	30	Typhus (?)
1/25/16	4035	43.5	3.4	6.6	0	10	Erythema nodosum
2/16/16	4166	45.9	5.4	5.2	0	15	Gout and alcohol
2/21/16	4180	38.3	5.6	4.7	0	10	Lymphatic leukemia
2/ 1/16	3281	38.5	27.8	5.8	0	65	Portal thrombosis
2/28/16	4197	38.3	5.6	6.0	0	15 amphoteric 20 total	Myxedema

of these tests are diabetes, chronic nephritis, pneumonia, acute articular rheumatism and several acute febrile conditions in the miscellaneous group. Cases of exophthalmic goiter, epilepsy, syphilis, chronic cardiac disease, subacute nephritis, lung abscess, and many in the miscellaneous group distinctly did not show any evidence of acidosis by these tests. The results in the cases of primary anemia, gastric cancer, Addison's disease, and cirrhosis of the liver were not so clearly defined and in some of the tests suggested a slight acidosis.

It is evident from these tests that the acidosis found in diabetes

is due to different causes, in part at least, from those that produce it in other conditions. It also seems likely that the acidosis met with in different diseases is due to various causes, since the response to these tests varies somewhat in the different conditions.

Of these tests, either the estimation of the carbon dioxid tension in the alveolar air or the so-called soda tolerance test showed variation from the normal in all the cases of acidosis. They also seem to be of value in detecting the degree of acidosis.

I wish to thank most heartily Miss Barker, Miss Russell and Miss Cate, who as laboratory assistants helped me in carrying out the various estimations on the air and urines.

Peter Bent Brigham Hospital.

SENSORY DISTURBANCES OF CEREBRAL ORIGIN

CONSIDERATION OF TYPES AND OF DIAGNOSTIC ELEMENTS *

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The character of sensory disturbances caused by cerebral lesions has always been a subject of considerable scientific interest because of its importance from the standpoint of localization. In one of my former studies[1] an attempt was made to investigate cerebral sensory disorders from an extensive clinical material. Although some of the conclusions reached then did not coincide with those of some workers in the same field, nevertheless the facts observed were sufficiently suggestive to question the views of those writers who considered their conclusions as definitely established.

Throughout the present work it has been my aim to approach the problem of sensory disturbances of cerebral origin on an anatomic basis. In order to be able to draw more stable conclusions, I submitted my patients, during several years of observation, to a rigorously uniform investigation. That is, every one of the patients was examined and reexamined repeatedly by the same methods and same procedures with regard to all forms of superficial and deep sensibilities. Every one of the cases came to necropsy. The uniformity of investigation was so strictly observed that some definite diagnostic inferences are permissible.

The forms of sensations which I have investigated are tactile sensibility, the sense of superficial pain, the thermic sense, the power of localization, the muscular sense, especially in passive movements, the sense of weight, the spacing sense, orientation sense, and stereognostic sense.

Tactile sensation was tested with absorbent cotton, which, in my judgment, is the best of all methods, as it enables one to detect the least impairment. The sense of pain was tested with my precision esthesiometer.[2] The thermic sense was tested with extreme heat and cold, usually very hot water and ice. The power of localization was tested by having the patient tell the spot touched while his eyes were closed (naming procedure) or by having him point out the touched spot after his eyes had been closed during the touching and after the impress made on the skin had disappeared (looking procedure). The

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1. Gordon, A.: Jour. Nerv. and Ment. Dis., March, 1903, xxx, 144.
2. Gordon, A.: Jour. Am. Med. Assn., 1909, lii, 1257.

muscular sense was tested only for passive movements. The patient's eyes being closed, extension, flexion and rotation of each segment of the fingers, of the arm, forearm, thigh, leg and foot were performed. The orientation sense was tested either with the finger-to-nose movements or with the Blix method. The latter consists of the following procedure: The patient is either sitting or standing, with his back against an immovable object. With a pencil in the hand to be examined, he touches a mark made on paper, which is placed in front of him. This is repeated several times with open and with closed eyes. The pencil leaves a mark each time it touches the paper. The distance between these marks and the fixed point will determine the degree of the error. The spacing test consists of touching with two points of the compass or with one point after another in close succession. In the first case the distance between the two points will determine the degree of ability or inability to recognize two points. In the second case, while one point is in contact with the skin, the other is rapidly brought down on the skin. The appreciation of a double contact is thus determined. The sense of weight was determined by placing light and heavy objects on the parts of the body to be examined. Cork, pieces of lead and coins were the objects used and comparisons were drawn between the appreciation of various weights on the sound and affected sides. The stereognostic sense was tested by asking the patient to recognize the form, consistence, also the material of which objects placed in the hand were made, finally the nature and their names. The same kind and number of objects were used in all the nine cases.

CASE REPORTS

CASE 1.—A man, aged 43, gave a negative Wassermann reaction. At necropsy a tumor was found (mixed cell sarcoma) in the left basal ganglia (Fig. 1). There had been characteristic general symptoms of intracranial pressure, namely, persistent headache, vertigo, vomiting and later in the course of the disease optic neuritis. There was also a hemiparetic condition on the right side, with an increased knee-jerk and doubtful Babinski, but a certain paradoxical reflex on the same side. Objective sensations on the affected side showed marked diminution of sensibility to touch, but pain and temperature senses presented an interesting peculiarity. If with a pin one attempted to provoke pain, the response of the patient was entirely out of proportion to the degree of stimulation. The reaction was excessive, the patient flinched considerably and complained of much pain. When a similar stimulus was used on the other side, the response was by far less marked. If, on the other hand, a mildly warm object was applied to the paretic side, a very pleasurable sensation was experienced by the patient on the tested surface. If a cold object was applied, the patient complained of a very disagreeable sensation. It was therefore evident that in spite of the affected side being anesthetic, there was hyperreaction to the sense of pain and temperature.

The deep sensibilities were markedly affected and among them especially posture, passive movements and pressure. The position in which various portions of the right arm and leg were placed was not recognized correctly by the patient; gross errors were made. Passive movements with the arm and legs

were also not accurately executed. Weights placed on the arm and leg were equally not correctly recognized. Astereognosis was also present in the right hand, probably because of the defect in the other deep sensibilities.

Subjectively, the patient complained of a constant pain in the right arm and leg, which was so persistent that it would not yield to the usual remedies. At times the pain was sharp and lancinating in character. To sum up, there was the "syndrome thalamique," such as described originally by Dejerine.

Fig. 1.—Tumor of left basal ganglia (Case 1).

Case 2.—A man, aged 38, a laborer, gave a negative Wassermann reaction. At necropsy (Fig. 2) softening of the entire left internal capsule, including its very posterior portion, also of the lenticular and caudate nuclei and of the adjacent portion of the optic thalamus. During life there was a total right hemiplegia, with aphasia, and conjugate deviation of head and eyes to the left.

There was a distinct diminution of the cutaneous sensibility to touch, pain and temperature over the entire paralyzed side. This condition was present not only shortly after the apoplectic insult, but also before the patient died. It is interesting to observe that the sense of pain was more affected than

the sense of touch and temperature, and this was alike over both arm and leg, while on the paralyzed side of the face all three superficial sensations were equally but slightly involved. The deep sensibilities were not involved, with the exception of the muscular sense, which was only slightly impaired. When one or two fingers or the entire hand of the paralyzed side were placed in a certain position, the patient sometimes (not always) made errors. When told of the error he soon corrected it. The involvement of the muscular

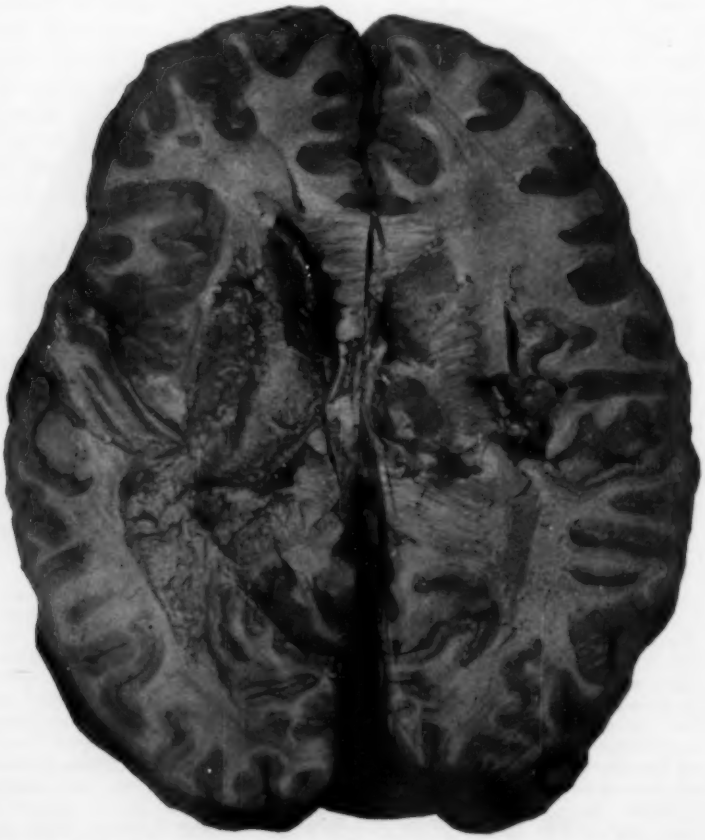

Fig. 2.—Softening of entire left internal capsule (Case 2).

sense was only distal, as this sense for the forearm, arm and shoulder remained intact. All other deep sensibilities, including the stereognostic sense, were normal. In view of the destruction of the carrefour sensitif in this patient, it is interesting to note that there was no contraction of the visual field or amblyopia on the affected side.

Case 3.—A man, 44 years of age, gave a negative Wassermann reaction. At necropsy there was found a gliomatous tumor in the left hemisphere,

involving the supramarginal gyrus, angular gyrus and the posterior third of the first and the second temporal convolutions, also a very small portion of the occipital lobe. On section the mass was shown to extend posteriorly into the occipital lobe and mesially as far as the posterior cornu of the lateral ventricle. The very posterior portion of the internal capsule and the corona radiata were involved by the tumor (Figs. 3 and 4).

Fig. 3.—Glioma in left hemisphere, involving supramarginal gyrus, angular gyrus, posterior third of the first and the second temporal convolutions (Case 3).

During life the patient presented verbal amnesia, alexia, paraphasia and paragraphia, also retinal hemorrhages with choked disk. The motor power and reflexes were normal and equal on both sides.

Fig. 4.—Same as Figure 3.

Sensations, superficial as well as deep, were normal on both sides during the entire time of the patient's illness. At no time was astereognosis observed. The destruction of the posterior portion of the internal capsule did not produce sensory disturbances. It is also significant that in spite of the marked involvement of the inferior half of the parietal lobe and in spite of consider-

able pressure on the upper portion of this lobe, the stereognostic sense was not disturbed.

Case 4.—A boy, 16 years of age, died from a tumor (round-cell sarcoma) wedged in between the frontal lobe and the insula of the left hemisphere and extending into the lateral ventricle in its anterior and lateral horns, compressing, displacing and destroying largely the surrounding tissue. Among the latter the lowest portions of the ascending frontal and parietal convolutions suffered considerably (Fig. 5).

Fig. 5.—Tumor (round-cell sarcoma) wedged in between the left frontal insula and the temporal lobes, penetrating the lateral ventricle (Case 4).

During life the patient presented headache, vomiting, vertigo, choked disk in both eyes, loss of knee-jerks and Achilles tendon reflexes on both sides, but Babinski and paradoxical reflexes were present on the right side. The face was slightly deviated to the left, and with this exception there was no paralysis or paresis on the right side.

On the entire right side there was a diminution of superficial sensations of all three forms, namely, touch, pain and temperature. There was no astereognosis or any other disturbance of the deep sensibilities.

CASE 5.—A man, 38 years of age, had a history of syphilis at the age of 23. Necropsy showed softening of the entire left internal capsule, lenticular nucleus, head and tail of caudate nucleus and the external capsule. The left optic thalamus was much paler than the right, and the part of it adjacent to the capsule also was softened (Fig. 6).

Fig. 6.—Softening of the entire left internal capsule (Case 5).

During life the patient presented a right hemiplegia with all the typical symptoms. Besides a partial alexia and partial verbal amnesia, which will not be described here, there was a decidedly marked diminution of sensations for touch, pain and temperature, also for localization. It is interesting to note that the pain sense was more involved than the touch and temperature senses, that the decrease of all sensations was more marked in the hand and foot than in the forearm and leg, and that in the latter two the diminished

sensibility was more pronounced than in the arm and thigh. The latter condition was parallel with the degree of loss of motor power in the corresponding segments of the affected limbs. The disturbance of the localization was more marked in the foot than in the hand, but an irregularity of this sensation was observed in the other parts of the right side. Thus, a touch on the right cheek was referred by the patient to the trunk, and a touch on the leg to the upper part of the thigh. Evidently the direction of pointing by the patient was toward the least-affected sensation.

Fig. 7.—Tumor of hypophysis; crura compressed; pons and medulla displaced (Case 6).

It is also interesting to observe that in spite of the destruction of the very posterior portion of the internal capsule the visual fields were not contracted, there was no amblyopia and no other special sense was involved.

Case 6.—A man, 31 years of age, had a diagnosis made of tumor of the pituitary body. The postmortem findings showed a large vascular tumor at the base of the brain extending backward as far as the foramen magnum and

forward to the sphenoidal fissure. The tumor consisted of two portions, the anterior being the smaller, the posterior the larger. Both covered the basal portion of the brain between the orbital lobes and the pons in the middle line. It pressed backward and disfigured enormously the pons and the structure of the posterior portion of the medulla, which could be seen also on microscopic sections. The crura cerebri were compressed and deformed. Microscopic sections showed, besides the angiosarcomatous character of the

Fig. 8.—Extensive hemorrhage over right parietal lobe (Case 7).

hypophysis, also a unilateral involvement of the pyramidal tract below the cerebral peduncles and spinal cord, but not in the internal capsule. In the posterior portion of the medulla and pons all the elements were hardly distinguishable; they were displaced and deformed (Fig. 7).

The patient showed a clinical history of headache and vertigo, right exophthalma, bitemporal hemianopsia, optic atrophy in left eye and optic neuritis in the right eye, attacks of unconsciousness, glycosuria, obesity, and infantile genitalia. Gradually a left descending hemiplegia developed and convulsive

attacks made their appearance on the paralyzed side. Soon difficulty of swallowing set in.

On the left side there was a sensory dissociation of almost syringomyelic type. The tactile sense was very slightly diminished, but the sense of pain was totally abolished. The senses of heat and cold were also dissociated, the sense of cold being entirely absent, so that ice felt warm while extreme heat was taken for tepid. Astereognosis was present in the left hand, patient

Fig. 9.—Extensive hemorrhage over right frontal lobe, encroaching on both rolandic convolutions (Case 8).

being unable to recognize the nature, shape and consistence of objects. Localization and pressure were but slightly involved. The above-mentioned diminution of the tactile sense was parallel with the loss of motor power, which was more marked in the distal than in the proximal segments of the limb and gradually decreased in intensity from the former toward the latter.

Case 7.—A boy, aged 17, with a diagnosis of cortical hemorrhage following trauma, came to necropsy. There was a large hemorrhage over the parietal

region of the right hemisphere. The overlying portion of the meninges was thickened (Fig. 8).

The clinical history showed that the boy fell down from a third story window. He was unconscious for five hours. There was no bleeding from the facial cavities. He was found lying on his right side. Twelve hours later, when consciousness had totally returned, he was examined. There was a slightly paretic condition of the left leg and arm, more of the first than of the latter. The left knee-jerk was slightly more marked than the right and the paradoxical sign was distinct and easily obtainable on the left. The Babinski was absent.

Fig. 10.—Subdural abscess over right frontal lobe, encroaching on the rolandic convolutions (Case 9).

There was a slight hemianesthesia of the left arm and leg to touch, pain and temperature. The deep sensibilities were considerably involved. Astereognosis was absolute for the left hand. The patient was unable to recognize the nature, consistence, form and material of objects placed in the left hand. Localization was markedly deficient in the left arm, hand and entire leg. Passive and active movements were equally inaccurate in the left arm and leg. Pressure, position and compass measurement were also involved, but less than the other deep sensibilities. Ataxia was distinct in his left hand, which could be demonstrated by the finger-to-nose movements and by the Blix method. The patient refused to be operated on. During his five weeks of life several examinations were made and the above sensory disturbances were found unaltered. The patient gradually developed fever and died in coma.

CASE 8.—A man, aged 32, a fireman, was injured while on duty. He was unconscious and a diagnosis of intracranial pressure in the right sensorimotor area was made.

At necropsy a large hemorrhage was found at the level of the right frontal lobe, encroaching also on the lower portions of both rolandic convolutions (Fig. 9). The patient lived two weeks. Operation was refused. He was conscious for ten days. The symptoms observed were headache and a paretic condition of the left arm and face. There was no abnormal reflex in the left leg, but the biceps and triceps reflexes of the left arm were exaggerated. The left lower face was slightly deviated to the right.

The cutaneous sensibility to touch, pain and temperature was unaltered. A slight ataxia was present in the left hand, especially in the finger-to-nose movements. Pressure, localization and compass measurements were decidedly defective in the hand, wrist and lower half of the forearm. The patient died in coma.

CASE 9.—A girl, aged 16, died from septic cerebral thrombophlebitis (pneumococcus) and abscess following an operation.

At necropsy a subdural abscess was found over the entire frontal region of the right hemisphere, encroaching on the rolandic convolutions (Fig. 10).

During life following the attack of influenza the patient developed headache, rigors, a temperature of 105, rigidity of the neck, abscess of the right upper lid and evidences of frontal sinusitis. A paretic condition of the left face, arm and leg was evident.

The sensations of touch, pain and temperature were all very slightly diminished. The left arm was ataxic and dysergic which could easily be seen in the finger-to-nose movements. Astereognosis was absolute, the patient being unable to recognize not only the form, shape and consistence but also the nature of the most ordinary objects. Position and muscular sense were defective. Other deep sensibilities, namely localization, compass measurements and pressure were all intact.

ANALYSIS OF THE CASES

Sensory Disturbances from Cortical Lesions.—In Case 4 there was a tumor pressing considerably on the lowest portions of the left ascending frontal and parietal lobes. While there was no paralysis of the right arm and leg, nevertheless there was a slight deviation of the lower portion of the face toward the left and the toe phenomenon was present. As to sensations, only the superficial ones were diminished on the entire right side. Here is an example of simultaneous involvement of the motor and sensory areas. In Case 7 a cortical hemorrhage occupied the right parietal lobe, with the result that the superficial sensations were but slightly involved, but all the deep sensibilities were strikingly affected. Among the latter the stereognostic sense especially, also the localization, muscular and orientation senses were particularly affected. Pressure, position and spacing senses were also, but to a lesser degree, involved. In Case 8 there was a hemorrhage over the right frontal lobe encroaching also on the lower portions of both rolandic convolutions. The superficial sensations were intact. Among the deep sensibilities, orientation, position, pressure, localization and spacing senses were defective in the left hand, wrist and lower half of the forearm. In Case 9 there was a subdural abscess

over the right frontal lobe encroaching on the rolandic convolutions. The superficial sensations on the left toe were very slightly diminished. Among the deep sensations, astereognosis, ataxia and dysergia were all marked on the left side; appreciation of position and muscular sense were defective, but localization, spacing and pressure were all intact.

Analysis of sensory disturbances produced by cortical lesions in these four cases demonstrates the fact that the superficial sensibilities were but slightly involved (Cases 4, 7 and 9) or not at all (Case 8); that tactile, painful and thermic senses usually run parallel in occurrence and intensity. The deep sensibilities were most constantly and always markedly affected (Cases 7, 8 and 9). Only in Case 4, in which a tumor pressed on the very lowest portions of the rolandic convolutions, the deep sensations alone were not involved. In all the three cases in which the deep sensations were defective position and muscular sense were invariably involved. Localization was intact only in one case out of three. Evidently the localization test is not always dependent on the power of an affected limb. The spacing sense was involved in but two cases. It is interesting to note that this sense runs parallel with the localization sense. In Case 9 the localization and the spacing senses were equally unaffected, but in Cases 7 and 8 they were equally affected. Astereognosis was present in two out of three cases and in both cases it was present, together with defects of some other deep sensibilities.

In considering the cortical sensory disturbances in their relation to motor phenomena we observe that in Case 4 the tumor pressed on the lower portions of both rolandic areas. Hemihypoesthesia was present, but with the exception of the left face, arm and leg, there was no motor paralysis, although Babinski's sign was present. In Case 7 motor and sensory hemianesthesias were simultaneously present. In Case 8 a hemiparetic condition was accompanied by disturbances of deep sensibilities on the same side. In Case 9 motor and sensory disturbances, superficial and deep, were equally present on the same side. We consequently find that in two cases disturbed superficial sensibility accompanied motor disorders, that in one case deep sensibilities were involved, together with the motor power, and in one case the superficial sensations were disturbed in the arm and leg, which had no loss of motor function, but there was loss of sensory and motor functions in the face. The question arises, have these findings any bearing on the sensory-motor localizations in the cortex? Do they contradict or confirm the generally accepted present view regarding the separate functions of the two ascending convolutions? In Case 4 both convolutions were compressed in their lowest portions. The tumor, being wedged in between the frontal lobe and the insula, was

located nearer the precentral than the postcentral convolutions. In spite of this the cutaneous sensibility was more involved than the motor power; there was no paralysis of the arm and leg, but a total hemianesthesia. In Case 8, on the contrary, a hemorrhage over the frontal lobe encroached also on the lower portions of both rolandic convolutions, a hemiparetic condition coexisting, with impairment of the deep sensibilities. In Case 9 there was a similar pathologic condition and sensorimotor disturbances were present. In this case all forms of sensation were involved. In these three cases both ascending convolutions were involved, consequently the problem of separate functions of the central convolutions cannot be decided from these findings. But Case 7 stands isolated from this point of view. Pathologically we find a hemorrhage covering the right parietal lobe close to the ascending parietal convolution, consequently at a distance from the ascending frontal. Clinically there were present, besides disturbed deep sensibilities, also a hemiparesis and a hemianethesia. Moreover, the degree of the loss of both kinds of function was parallel. Here the pressure on the cortex was superficial, as sections of the affected part of the brain failed to reveal any changes in the subcortical tissue of the involved area as well as of the ascending frontal convolution. To reconcile the clinical findings in this exceptional case with the generally admitted view concerning the separate function of each rolandic convolution is quite difficult. A similar difficulty is experienced in the interpretation of many similar cases reported by competent authors. I mention at least the well-known case of Horsley (1909), in which extirpation of the ascending frontal convolution was followed by sensorimotor disturbances.

If we turn our attention to the deep sensibilities, we find in Case 7 all deep sensibilities disturbed. Pathologically the parietal lobe proper was involved. In Case 7, in spite of involvement of the lower portions of the ascending convolutions, the superficial sensations were intact and some of the deep sensibilities suffered, namely, orientation, position, pressure, localization and spacing senses. In Case 9 the pathologic condition was identical with that of Case 8 and we find a slight hemianesthesia, but a pronounced disturbance of some of the deep sensibilities, including the stereognostic sense. It is evident that all deep sensibilities are affected in cases of a lesion in the parietal lobe (Case 7), but some of them may be affected in cases of lesion in cortical areas other than the parietal, such as the frontal lobe and the two central convolutions. As far as astereognosis is concerned, we are in possession of a large number of facts, all tending to prove that the parietal lobe is not the only cortical region controlling the stereognostic function. Cases 8 and 9 are also striking examples of this contention. As to the point of view of stereognosis being a faculty

dependent on the integrity of other sensibilities, it is not tenable, as there are cases on record in which the stereognostic faculty was disturbed or abolished and other sensations were intact.[3]

Sensory Disorders from Capsular Lesions.—In Case 2 there was an extensive softening of the entire left internal capsule, also of the adjacent portion of the optic thalamus. The superficial sensibilities were involved over the entire paralyzed side. Among the deep sensations, only the muscular sense was slightly impaired, the others being intact. In Case 3 a gliomatous tumor involved in the left hemisphere the supramarginal gyrus, angular gyrus, and the posterior third of the first and the second temporal convolutions. On a transverse section we see the posterior portion of the internal capsule destroyed by the tumor. Apart from the special manifestations corresponding to the involved special centers, there were no sensory or motor disturbances whatever. It is also interesting to note that in spite of considerable pressure on the parietal lobe there was no trace of symptoms referable to the deep sensibilities, including the stereognostic sense. In Case 5 there was a softening of the entire left internal capsule and of the adjacent portion of the optic thalamus. The patient presented a right hemiplegia and hemianesthesia for touch, pain and temperature and also for localization. The degree of sensory diminution corresponded to the degree of diminution of the motor function, although the impairment of the localization sense was more marked in the foot than in the hand.

An analysis of these three anatomoclinical cases shows that in Cases 2 and 5 sensory and motor disturbances were concomitantly present on the same side; that in both cases the superficial sensibilities almost alone were affected; that very few of the deep sensibilities were involved, namely, muscular sense in one case and localization in the other case; that in both cases the posterior portions of the internal capsule were affected and that in both cases the adjacent portion of the thalamus was involved. In Case 3 the lesion was cortical as well as capsular. Curiously enough, the cortical lesion (parietal lobe) did not disturb the deep sensibilities and the capsular lesion (posterior limb) did not produce sensory symptoms. If, in accordance with the teaching of Charcot concerning the carrefour sensitif, we are to expect hemianesthesia of the cutaneous and deep sensibilities and disturbance in the domain of the special sensorium, particularly contraction of the visual fields with amblyopia on the anesthetic side, the three observations recorded speak decidedly against the alleged function of the carrefour sensitif. In Cases 2 and 5 there was only hemianesthesia of the superficial sensations and no involvement whatever of the

3. Gordon, A.: Rev. Neurol., Sept. 30, 1910, p. 301.

special senses, and in Case 3 the posterior portion of the internal capsule was destroyed and sensory manifestations of any kind were conspicuously absent. The three cases seem to favor strongly the contention that while the internal capsule possesses a sensorimotor function, its very posterior portion does not possess the exclusive sensory function, as advocated by Türck and Charcot. This is particularly seen from Case 3. The concomitance of a lesion in that portion of the thalamus which is adjacent to the internal capsule is very significant, as it leads to the possibility if not probability that the sensory disturbances accompanying motor paralysis are due to the involvement of the corticipetal or thalamocortical fibers, which, together with the projection fibers, enter into the formation of the posterior segment of the internal capsule.

Sensory Disturbances from Lesions of the Optic Thalamus.—In Case 1 (tumor in basal ganglia in left hemisphere) there was a hemiparesis and sensory disturbances on the same side. Touch sense was diminished, but pain sense was increased (hyperalgesia); warmth produced a pleasurable sensation, cold a disagreeable sensation. On the same side some of the deep sensibilities were involved, namely, position, muscular sense, stereognostic sense and pressure. Gross errors were made by the patient at each repeated test. There was also considerable subjective pain in the right arm, which was unusually persistent.

The striking peculiarity about this case is the dissociation of the superficial sensibilities and the excessive response to painful stimuli and to cold. The existence of hyperalgesia on the anesthesic side is unusual, although sensory disorders of this character in lesions of the lateral zone of the optic thalamus have been reported by Edinger[4] and Roussy.[5] The pleasurable sensation to warmth and disagreeable sensation to cold form another peculiarity in this case. The fact that these phenomena, together with the above-mentioned hyperalgesia, have been totally absent in all the other cases of my series renders the condition quite suggestive, inasmuch as it may be considered characteristic of thalamic lesions.

In addition to these manifestations the marked involvement of several forms of deep sensibilities and the spontaneous pain on the anesthetic side constitute a separate group of sensory phenomena which are not encountered in cortical or capsular lesions. They are therefore pathognomonic of the thalamic syndrome originally described by Dejerine.

4. Edinger: Deutsch. Ztschr. f. Nervenh., 1891, i, 262.
5. Roussy: Neurol. Rev., 1909, xvii, 301.

Sensory Disturbances from a Peduncular Lesion.—In Case 6 a tumor of the pituitary body disfigured the crura and all the elements in the posterior portions of the pons and medulla. The superficial sensations on the hemiplegic side presented a dissociation of a syringomyelic type with regard to touch and pain and also a thermic dissociation, the sense of cold being absent and extreme heat being taken for tepid. Among the deep sensibilities, the stereognostic sense was markedly impaired. Localization and pressure were but slightly involved. There was no crossed hemiplegia or crossed hemianesthesia. The cranial nerves were not invaded by the tumor. The pressure by the latter backward was such that it disfigured and displaced the crura and the pons, but did not completely destroy them. In this case we have, therefore, a conspicuous sensory symptom dissociation in the superficial sensibilities, with marked disturbances in the deep sensibilities. The latter were more pronounced than the former. The sensory disturbances were present on the side on which the motor function was impaired.

DIAGNOSTIC DEDUCTIONS

A review of the forms of impaired sensibility in various cerebral lesions demonstrates the fact that the superficial sensations are to a greater or lesser extent involved in all the lesions of the brain considered here. The capsular lesions give the most pronounced and the most persistent disturbances in the touch, pain and temperature senses. The least involvement is seen in the cortical cases. The three senses run parallel in degree and extent. A distinct dissociation is seen in the peduncular lesions and this dissociation is analogous to the syringomyelic type. In the thalamic cases there is also a dissociation, but of a special kind, namely, a diminution of touch sense, pleasant feeling from warmth and disagreeable feeling from cold. Disturbances in the deep sensibilities were found in all varieties of lesions considered here. The most constant and most extensive variety was the cortical one. Next in order of degree of involvement is the thalamic kind. Among all forms of deep sensibilities position and muscular sense were most frequently affected. These were disturbed in all except in the peduncular variety. The localization sense was found altered next in frequency. Astereognosis comes next in order of frequency.

In spite of this apparent regularity in sensory impairment, certain exceptions were nevertheless present. Special emphasis is laid on Case 3, in which an involvement of the parietal lobe and a destruction of the posterior portion of the internal capsule gave no sensory disturbances of any sort. In capsular lesions in which the superficial sensibility is so conspicuously involved there was also impairment of some deep sensibilities. In the peduncular variety the deep sensibilities were

more involved than the superficial ones. Astereognosis, which has been looked on as a symptom of a lesion in the parietal lobe, was present here, not only in the cortical, but also in the thalamic and peduncular, variety.

On the other hand, in Case 3 the lesion of the parietal lobe gave no disturbance of the stereognostic sense. Similarly, in the case reported by me[6] in 1908 a bullet entered the left parietal region and subsequently an operation with extensive destruction in the same area did not cause a loss of the stereognostic sense or of any other form of sensations. Among other authors, Verger and Abadie,[7] for example, published in 1900 the history of a case in which a sarcoma of the dura compressed the entire parietal lobe so that the cortex was markedly flattened and still the general sensibility and the stereognostic sense remained intact. In connection with these clinical irregularities, which are usually called exceptions, it may not be superfluous again to call attention to Case 7, in which a cortical hemorrhage strictly confined to the parietal lobe, but close to the ascending parietal convolution, gave place not only to an impairment of the superficial sensibilities, which was to be expected, but also to a motor hemiplegia, although the hemorrhagic area was far removed from the anterior central convolution.

The problem of sensibility of cerebral origin, as studied from a clinical standpoint but verified by means of anatomic material, establishes the existence of types of sensory disorders more or less distinct from each other. The nine anatomoclinical cases described here corroborate in a general way the findings of some authors, yet the exceptional features are sufficiently conspicuous to emphasize the fact that certain conservative reservations must always be made when diagnostic inferences present themselves. Literature is abundant with examples which militate against the generally adopted views. Exclusivism is a method which may be damaging to diagnostic investigations.

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6. Gordon, A.: Med. Rec., New York, April 18, 1908, lxxiii. 648.
7. Verger and Abadie: Bull. Soc. d'anat. de Bordeaux, April 30, 1900, p. 347.

THE ACTION OF THE VARIOUS FEMALE REMEDIES ON THE EXCISED INTESTINE OF THE RABBIT*

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In a recent communication[1] was presented the pharmacologic action of the so-called female remedies on strips of the excised uterus of the guinea-pig. Many of them depressed the activity of the strips, but it was suggested that this effect might have been nothing more than an action on nonstriped muscle in general and that it was in no sense specific to the uterus muscle. To investigate this question experiments have been made on other forms of smooth muscle, namely, strips of intestine of the rabbit and the arteries of the kidneys of dogs. The results of this work show that these drugs, when active, do not act specifically on the uterus.

The experiments on the intestine were made in a similar manner to the experiments on the excised uterus of the guinea-pigs; a segment of the small intestine of the rabbit, about 2 or 3 cm. long, was attached to a muscle lever and immersed in a well-aerated bath of Tyrode solution and the contractions recorded. Contractions are usually started shortly after placing the strips in the bath and continue fairly uniformly for some time. After obtaining a suitable control tracing the drugs to be examined were added to the bath to make a concentration of 1 to 1,000 as a rule, but at times a 1 to 2,000 or 1 to 500 solution. The same fluidextracts of the drugs were used in this work as in the previous work on strips of the uterus.

The Experimental Results: The manifestation of the activity of the drugs was practically the same as on the strips of the uterus, namely, the chief function affected was the amplitude of the excursions and, secondarily, the rate and the tone. Further, the results of the action were practically identical with the results on the uterine strips. The drugs that depressed the excursions, and the degree of their action, were practically the same in each series. The single drug that put the strips of uterus into tonic contraction had a somewhat similar action on the intestinal segments. The inactive drugs, with but a single exception (*Chamaelirium luteum*), were the same in each series.

The following drugs lowered the amplitude of the excursion and,

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* From the Pharmacologic Laboratory, University of Nebraska, College of Medicine, Omaha.

1. Pilcher, Burman and Delzell: THE ARCHIVES INT. MED., 1916, xviii, 557.

secondarily, decreased the rate and lessened the tone in some instances: Jamaica dogwood (*Ichthyomethia piscipula,* Fig. 1), pulsatilla (*Pulsatilla pratensis*), unicorn root (*Aletris farinosa,* Fig. 2), and figwort (*Scrophularia marylandica*) were the most active, and while there were occasional segments that were but slightly depressed by these drugs, the contractions of the majority of them were usually inhibited shortly after adding the drug to the bath. Lady's-slipper (*Cypripedium pubescens*) and valerian (*Valeriana officinalis,* Fig. 3) were somewhat less active, but the oil of valerian was depressant in dilutions of 1 to 100,000 (Fig. 4). Skullcap (*Scutellaria lateriflora*), wild yam (*Dioscorea villosa*), liferoot (*Senecio aureus*) and false unicorn root (*Chamaelirium luteum*) possessed a slight depressant action; false unicorn root at times was rather active and this is the only drug whose action differed from that on the uterus, on which it had no effect.

Fig. 1.—Ichthyomethia piscipula (Jamaica dogwood) on strip of rabbit intestine, applied at "5," to make a 1 to 1,000 solution.

Blue cohosh (*Caulophyllum thalictroides,* Fig. 5) inhibited the contractions and left the tone somewhat above the normal, but did not put the strips into tonic contraction as it did the strips of uterus.

The following drugs were practically void of action: blessed thistle (*Cnicus benedictus*), cramp bark (*Viburnum opulus*), black haw (*Viburnum prunifolium*), maple bark (*Acer spicatum*), passion flower (*Passiflora incarnata*), motherwort (*Leonurus cardiaca*) and squaw vine (*Mitchella repens*).

The Experimental Data: Pulsatilla was depressant in concentrations of 1 to 2,000 and the depression increased with the concentration. In two exceptional instances there was practically no effect with the 1 to 1,000 solution. In others the decrease in amplitude was quite marked. The rate was usually not altered appreciably. In all, sixteen experiments were made.

Aletris in the 1 to 1,000 solution usually stopped the contractions within a minute or two. Weaker solutions were also effective in the majority of cases.

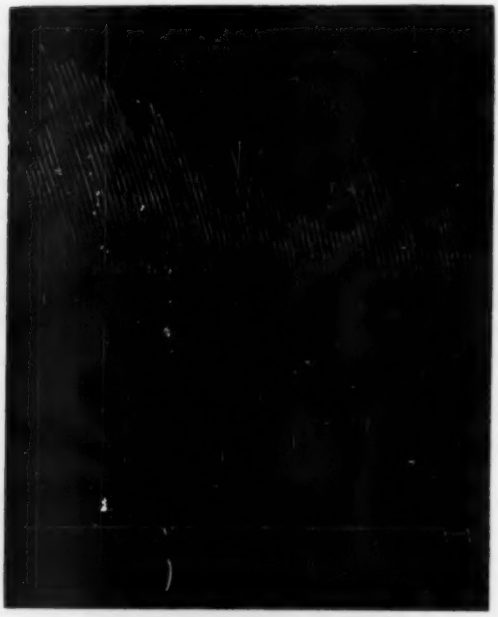

Fig. 2.—Aletris farinosa (unicorn root) on strip of rabbit intestine, applied at "1," to make a 1 to 2,000 solution.

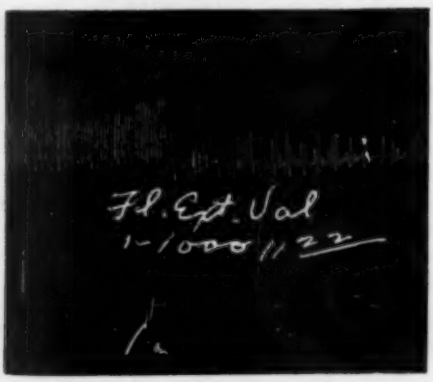

Fig. 3.—Valerian on strip of rabbit intestine, applied at "1," to make a 1 to 1,000 solution.

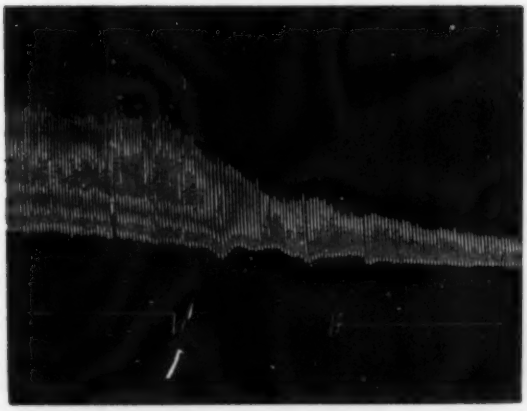

Fig. 4.—Oil of valerian on strip of rabbit intestine, applied at "1," to make a 1 to 100,000 solution.

Fig. 5.—Caulophyllum thalictroides (blue cohosh) on strip of rabbit intestine, applied at "2," to make a 1 to 1,000 solution.

The tone was not lowered below the normal diastolic level. Fourteen experiments were made.

Ichthyomethia was used in but three experiments, as each time the concentrations ceased shortly after adding it to make a 1 to 1,000 concentration.

With scrophularia, in a large number of experiments, there was a uniform decrease in the amplitude of the excursion. The tone was frequently lowered, but the rate was not materially altered.

With cypripedium the amplitude was usually decreased with the 1 to 1,000 solution and constantly with the stronger ones. The action was less than with the drugs mentioned above.

Valerian was active in the concentration of 1 to 2,000 as well as with the 1 to 1,000. In five experiments with each dilution the amplitude was lessened in about one third of the experiments with a 1 to 100,000 solution, and more and the tone quite frequently lowered also. The oil of valerian was depressant frequently with the 1 to 50,000. Stronger solutions were not used, as it was the experience that strips of guinea-pig uterus did not recover from the depressant action of stronger solutions of oil.

Scutellaria and *Senecio aureus* were but slightly and inconstantly depressant with even the 1 to 500 solution.

Chamaelirium quite frequently lowered the amplitude of the excursions, but often was not effective. It is the only member of the series that exhibited a different action on the intestinal and uterine strips, for there was practically no action on the latter; however, the depression of the intestinal strips was not of sufficient degree to warrant attention.

Caulophyllum was quite active in depressing the amplitude of the excursions with the 1 to 2,000 solution, but had little action on the tone, differing in this respect from the action on the strips of uterus. On adding the drug the excursions were rather promptly lessened, but the tone remained just a little above the original diastolic level, whereas strips of the uterus were put into tonic contraction, frequently considerably above the previous maximal level.

The Inactive Drugs: As the drugs that were inactive on the uterus were inactive on the intestinal strips, but two or three experiments were made with each of them. In three of seven experiments with *Viburnum prunifolium* there was slight depression of the amplitude, but this was so insignificant and inconstant as to be deemed negligible.

The experiments on arteries: To test the effect of these drugs on the smooth muscle of arteries the kidneys of a number of dogs were perfused with concentrations of 1 to 500. As is well known, vasoconstricting drugs decrease the vein flow of perfused kidneys and vasodilators increase the flow. The kidneys were perfused with a 1 per cent. solution of sodium chlorid until the outflow was fairly constant, and then a 1 to 500 solution of a drug was substituted. The following drugs were examined in this manner and none of them materially altered the perfusion rate, indicating that there was no action on the vessels: unicorn root, Jamaica dogwood, pulsatilla, figwort and blue cohosh.

COMMENT

The results of this work indicate that the members of the group of female remedies that act on strips of uterus exhibit practically an identical action on strips of intestine, both in manner and degree of action. The other drugs of the group have no effect on either uterus or

intestine. This shows that they in no sense act specifically on the uterus. While there are no experiments on the effect of these drugs on the intact uterus and intestine, it is highly probable that doses that would influence the movements of the uterus would have the same effect on the intestinal movements. Any beneficial action they might exhibit on the uterus—but such action is not conceivable—would be offset by the effect on the intestines, such as cessation of peristalsis, or in the case of one of the drugs, by a tonic contraction of the intestines.

CONCLUSION

The drugs in the list known as female remedies exhibit practically the same action on the excised intestine of the rabbit as on the excised uterus of the guinea-pig, showing that their action is in no sense specific to the uterus.

The following depress the intestinal strips actively in the concentrations used: Jamaica dogwood, pulsatilla, unicorn root and figwort; while valerian (the oil is very depressant) and lady's-slipper are less active; and skullcap, wild yam, liferoot and false unicorn depress very slightly.

The following are practically devoid of action: blessed thistle, cramp bark, maple bark, black haw, passion flower, motherwort and squaw vine.

They have no effect on the smooth muscle of arteries in rather concentrated solutions.

A STUDY OF A CASE OF INTERMITTENT COMPLETE DISSOCIATION OF AURICLES AND VENTRICLES PRESENTING UNUSUAL FEATURES*

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In the case which we are about to report the following features will receive consideration: a conduction defect in the main stem and the right branch of bundle demonstrable at all periods of associated contraction of auricle and ventricle; transient periods of complete dissociation of auricle and ventricle, some of which were closely associated with digitalis administration; a rate of ventricle which exceeded that of the auricle in all periods of dissociation, except one; the occurrence of frequent junctional premature beats during periods of normal sequence of contraction; variations observed in ventricular complex; the apparent relation of digitalis administration with disturbances of mechanism as above noted, and with the degree of heart failure as estimated at a given time.

Case History.—F. W., aged 61, a real estate broker, was admitted to the St. Francis Hospital on Nov. 17, 1915. He was transferred to the medical service two days later, at which time his chief complaint was "asthma," a term which he applied to severe, acute attacks of breathlessness, accompanied by productive cough, wheezing and great physical and mental distress. These attacks were of brief duration. They had occurred with increasing frequency during the previous two years, and were more likely to occur at night. During the preceding year the patient had noticed a steadily decreasing field of effort. Thus, dyspnea on severe exertion later became dyspnea when the patient was at rest. There had been a coincident loss in weight, stated at about 25 pounds. During the three days previous to admission, the patient had received a total of 3 c.c. of tincture of digitalis. No history of previous digitalis administration could be elicited.

The past history was negative in regard to the members of the rheumatic group and to syphilis. The patient had used tobacco and alcohol, but both in moderation.

The physical examination on admission showed that the patient was in marked distress because of dyspnea of such grade as to require the constant use of a back rest. His color was pale, lips cyanotic; the venules were distended over the nose and the cheeks; the carotids were throbbing; there was marked pulsation of the jugulars; the apex was displaced downward and to the left. No gross arrhythmia was noted at this time, but the rate of pulse varied widely: thus, it was between 100 and 120 while the patient was free from his attacks of breathlessness. During such attacks the rate increased to 150. The palpable arteries were moderately sclerotic. The blood pressure was 140 systolic and 70 diastolic. The area of precordial dulness was increased, the right border

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* From the University of Pittsburgh, School of Medicine.
* Read before the American Therapeutic Society, June 10, 1916.

of dulness being 4.5 cm. to right of the midsternal line at the fourth interspace, and the left border of dulness 14.5 cm., in the sixth interspace. There was no evidence of pericardial effusion. Mitral insufficiency was evidenced by the constant presence of a musical systolic murmur with the point of maximum intensity at the apex, and with transmission upward and to the left as far as the posterior axillary line, the second sound in pulmonary region being markedly accentuated. Edema of the lungs was present. There was marked subcutaneous edema over the sternum, sacrum and tibiae. The liver was enlarged and tender, the lower border extending 4 cm. below the costal margin in the midclavicular line.

An examination of the cardiac mechanism (Fig. 1) disclosed right bundle defect and an *As-Vs* interval of 0.3 of a second in Lead II. The urine was of low specific gravity, with a trace of albumin and a few hyaline and granular casts. The blood Wassermann reaction was negative.

Subsequent Course of Case.—The patient remained in the hospital twenty-eight days. During all of this period decompensation was marked, while at times it became acute and very alarming. Nevertheless, the mass movement of blood gradually improved under rest and symptomatic treatment. During the last few days in the hospital the patient became dissatisfied with his environment, and strongly objected to the taking of tracings and electrocardiograms.

Electrocardiographic records were made on six different occasions. In the first four of these records, made at intervals of three days during a period of twelve days following admission, association is shown (Figs. 1 and 2). The records made on December 13, twenty-six days after digitalis administration, show periods of complete dissociation (Fig. 4). Records made on the following day show normal sequence of chamber contraction.

On Dec. 16, 1915, the patient left the hospital against advice, and for a brief period was under the care of one of us. Subsequently, his family decided to remove him from medical treatment. Thereafter, all restriction of effort was apparently disregarded. The patient went up and down stairs several times daily, and took a number of rather long walks. Within a short time decompensation became grave, and the "asthmatic" attacks reappeared.

On Feb. 3, 1916, one of us was again called to see the patient at his home. He was found to be in a state of extreme agitation and exhaustion. Decompensation was profound, the evidence being orthopnea, a barely perceptible radial pulse, pulmonary edema, and general venous stasis. The lower border of the liver was demonstrable at the level of the umbilicus in the right midclavicular line. At this period digitalis administration was begun in the full realization of the possibility of the conduction defect being increased by its use. A total amount of 4 c.c. was given during a period of three days, and the patient was urged to return to the hospital that possible unfavorable digitalis effect might be promptly recognized. He was readmitted on February 6, and on both February 7 and 8 he received 2 c.c. of tincture of digitalis.

Venesection was performed on February 7, with temporary relief of stasis. On February 9 no digitalis was given. Electrocardiographic records made on February 8 and 9 (Fig. 5) showed complete dissociation. It is to be noted that at this period the patient had taken a total of 8 c.c. of tincture of digitalis. Early in the morning of February 10 venesection was again performed. On this day the patient's condition became so alarming that 0.4 mg. of strophanthin was given intravenously, and the patient was put on 4 c.c. of tincture of digitalis daily. Following strophanthin there was marked improvement of the patient's condition, both subjective and objective.

Electrocardiographic records (Fig. 6) made six and one-half hours after strophanthin injection showed a normal sequence of chamber contractions, but varying *P-R* intervals. On the following day, February 11, periods occurred of both normal sequence and complete dissociation. On the records showing normal sequence a great number of junctional premature beats is shown (Fig. 7). On Feb. 12, 1916, the digitalis was cut to 2 c.c. daily and continued

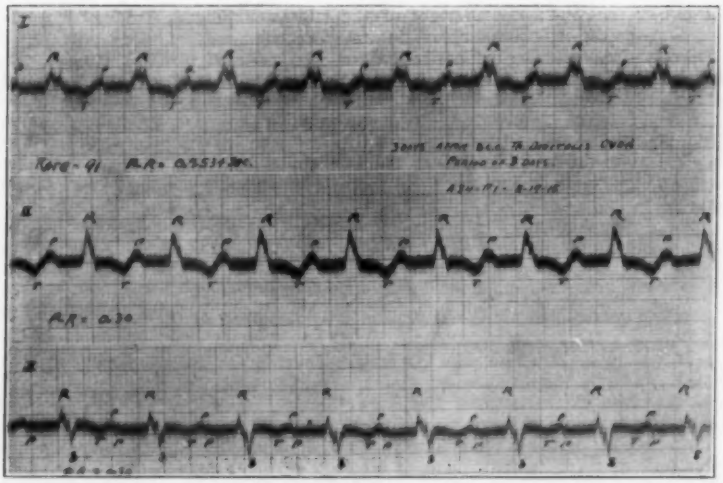


Fig. 1 (Plate 1).—Nov. 19, 1915. Right branch bundle defect and prolongation of *P-R* interval are shown. The heart is responding to impulses originating in the sino-auricular node. A condition of 2 to 1 block cannot be excluded in this electrocardiogram. This plate was taken three days after digitalis had been discontinued, the total amount ingested having been 3 c.c. of the tincture administered over a period of three consecutive days.

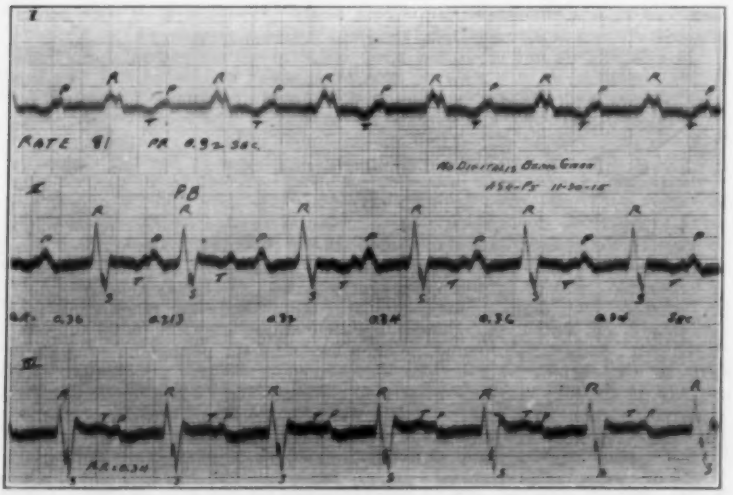


Fig. 2 (Plate 5).—Nov. 30, 1915. Right branch bundle defect, prolongation of *P-R* interval; sino-auricular rhythm; 2 to 1 block excluded by failure of curve to space for buried *P*, while furthermore, iso-electric line following junctional premature beat in Lead II is not broken by *P* complex.

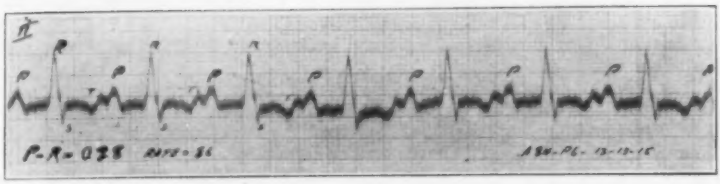


Fig. 3 (Plate 6).—Lead II. Dec. 13, 1915. Heart responded to impulses originated in sino-auricular node.

Fig. 4 (Plate 7).—Taken on same day as Figure 3. In Figure 3 the sino-auricular node is dominant for the whole heart. In this figure complete dissociation is shown over the first four cycles, after which the *P-R* interval remains constant.

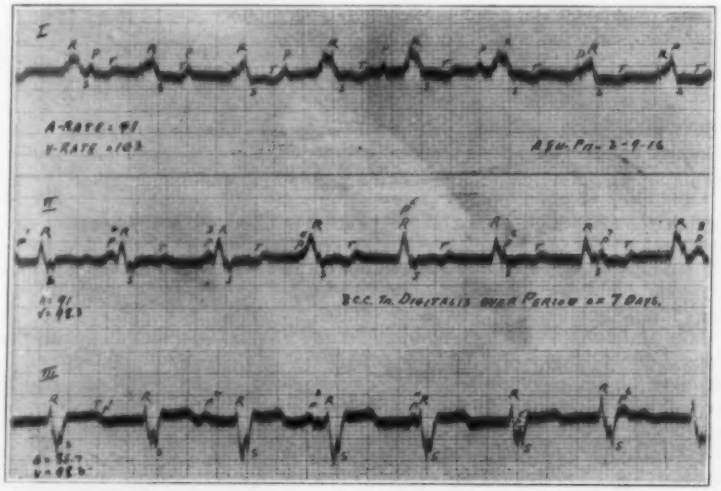


Fig. 5 (Plate 11).—Feb. 9, 1916. This plate was taken the third day after the second admission. The patient had taken 8 c.c. of tincture of digitalis over a period of seven days. Complete dissociation is shown; the ventricular rate is uniformly more rapid than the auricular. (A like mechanism is shown on a bromid strip made on the same day, over a period of forty-eight seconds.)

at this dosage until February 18, when it was entirely discontinued. On February 13, 14 and 15 electrocardiographic records (Fig. 8) showed complete dissociation; on February 16 the normal sequence of chamber contraction had been resumed (Fig. 9).

No digitalis was given from February 19 to March 3; but during this period there was a gradual rise of pulse rate, with an increasing deficit between fluid intake and output (Fig. 17). March 3 the condition of the patient was again very unsatisfactory. Cheyne-Stokes respiration was present even while the patient was awake. All electrocardiographic records made during this period had shown normal sequence of chamber contractions (Fig. 10). Nevertheless, in view of the urgency of the symptoms and of previous apparently favorable clinical results of digitalis administration, a further course of the remedy was now instituted. On March 4 the patient was given strophanthin, 0.4 mg. intravenously, and put on 4 c.c. tincture of digitalis daily. The digitalis was continued until the 13th, when it was cut to 2 c.c. daily and continued until the 19th. Electrocardiographic records made on the 10th, 11th, and 18th of

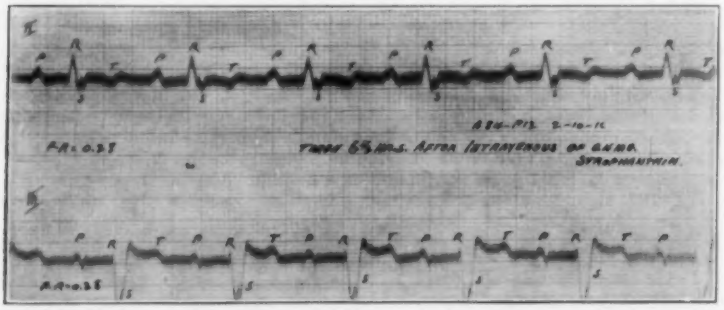
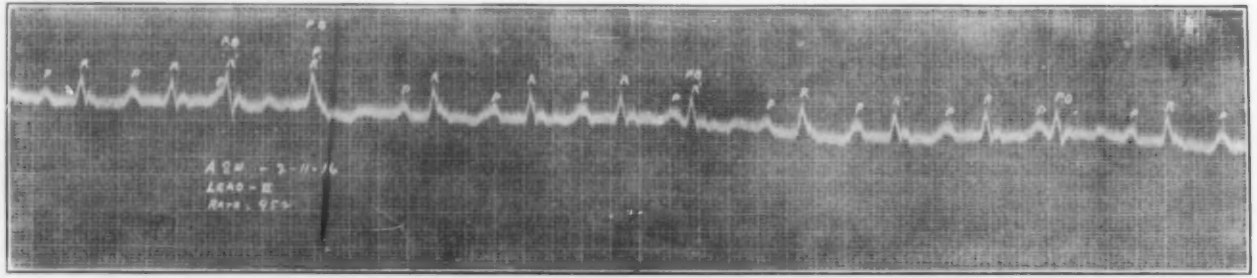


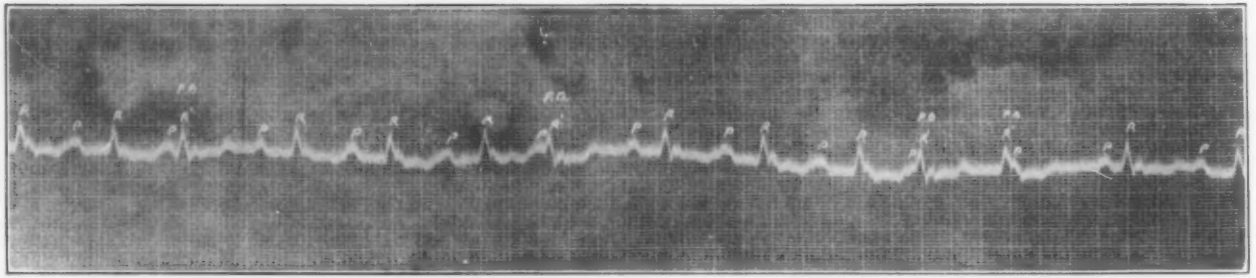
Fig. 6 (Plate 12).—Feb. 10, 1916. This plate was taken six and one-half hours after the intravenous injection of 0.4 mg. of strophanthin. There is apparent normal sequence of chamber contraction. Leads II and III are shown. The records made on the previous day (Fig. 5) had shown complete dissociation.

March showed complete dissociation (Fig. 11). This dissociation, unlike that exhibited earlier in the case, presented a ventricular rate somewhat below that of the auricles. From March 18 to March 22 the patient was given a prescription containing 0.2 gm. each of powdered digitalis, powdered squills and blue mass.

On March 23 he was again put on tincture of digitalis, 4 c.c. daily, and the foregoing prescription was discontinued. The last electrocardiographic records made on March 4 (Fig. 12) showed complete dissociation. During this second period of digitalis administration the fluid intake and output curves again approximated each other (Fig. 17), and there ensued marked improvement in the circulation. The subjective symptoms also abated to such a degree that on March 26 the patient insisted on leaving the hospital, stating that he was feeling too well to stay there. Heart failure was still marked at the time he passed from observation. We are informed he made a journey to and from Atlantic City in safety, but that he died seven weeks after his return. Unfortunately no records of cardiac mechanism were made after he left St. Francis Hospital, and necropsy was not obtained.



Part 1.



Part 2

Fig. 7 (Bromid Strip 5).—Feb. 11, 1916. Normal sino-auricular rhythm interrupted by frequent premature beats originating in junctional tissue.

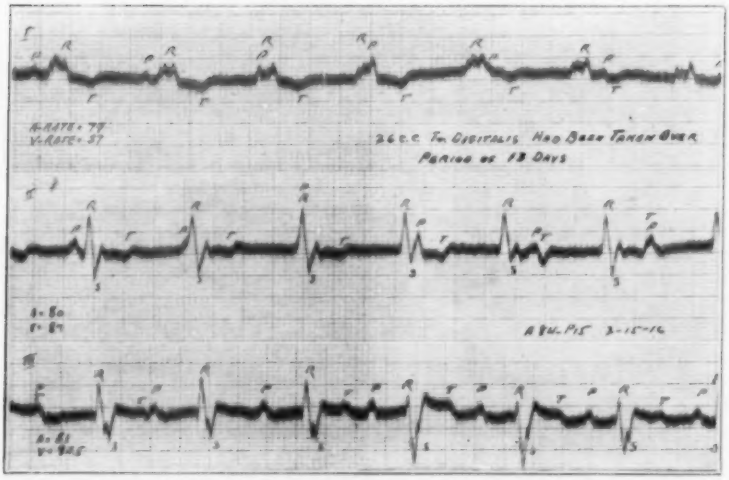


Fig. 8 (Plate 15).—Feb. 15, 1916. Complete dissociation, the ventricular rate being more rapid than the auricular. In Lead III the first three ventricular complexes suggest right preponderance; the three following complexes are suggestive of left preponderance, while the last *R* deflection appearing in this lead shows a tendency to return to contour noted in the first three complexes.

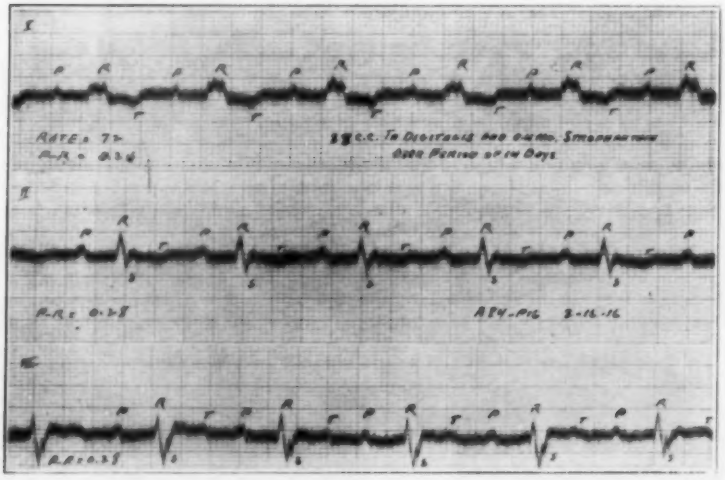


Fig. 9 (Plate 16).—Feb. 16, 1916. Normal sequence of chamber contractions is shown. A record made the day before (Fig. 8) shows complete dissociation. At this time the patient was being given tincture of digitalis, 2 c.c. daily.

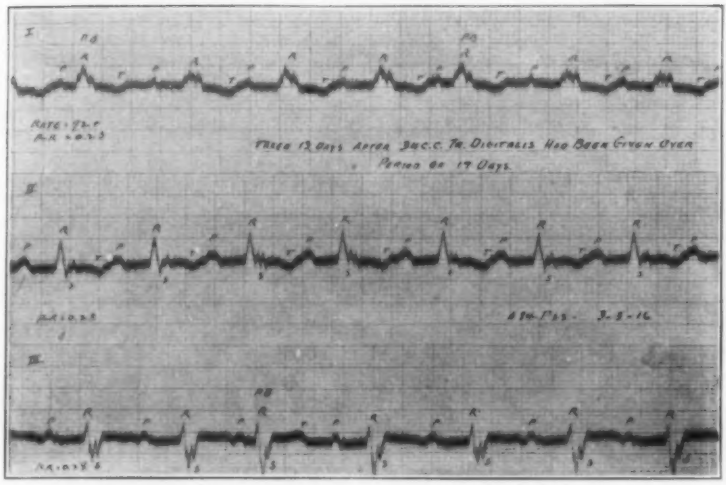


Fig. 10 (Plate 23).—March 3, 1916. Seven electrocardiograms taken since February 16 showed normal sequence of chamber contraction. No periods of dissociation were observed. The patient had had no digitalis for thirteen days. The clinical condition of the patient on this day was very unsatisfactory. Digitalis was resumed the following day. (See Figure 17.)

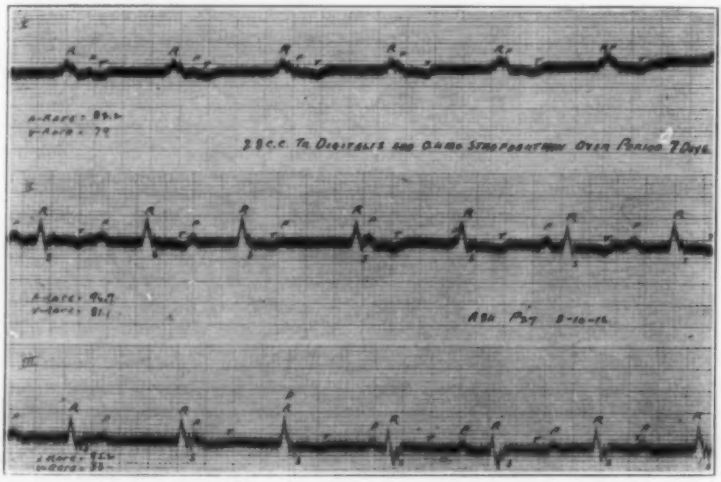


Fig. 11 (Plate 27).—March 10, 1916. It will be noted that the auricular rate is more rapid than the ventricular in all leads. The total digitalis intake at this period is indicated on the electrocardiogram.

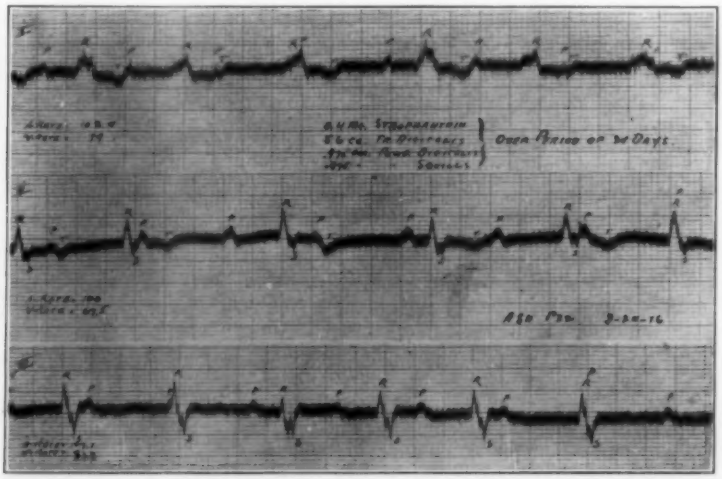


Fig. 12 (Plate 32).—March 24, 1916. Complete dissociation; auricular rate more rapid than ventricular; ventricular arrhythmia. Compare the total digitalis intake at this period with that noted in Figure 11, at which time the ventricular arrhythmia was less marked.

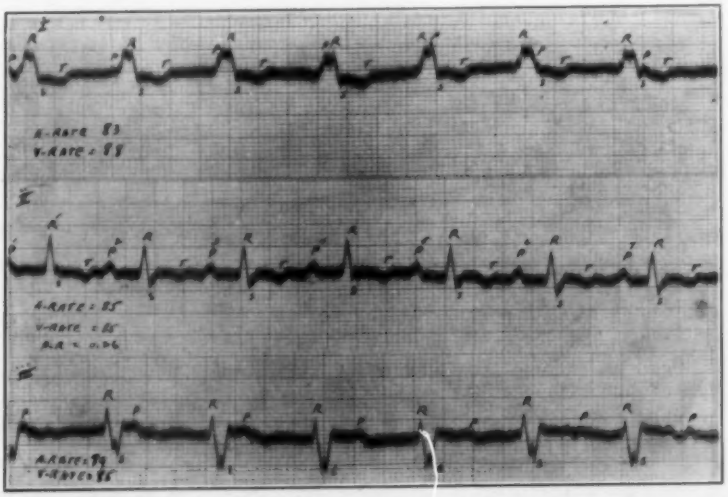


Fig. 13 (Plate 13).—Feb. 11, 1916. This curve shows complete dissociation in Leads I and III and normal sequence in Lead II. *R'* in Lead II is probably an ectopic ventricular beat replacing the normal ventricular response.

COMMENT

Stem and branch bundle defect may be recognized in all curves showing association (Fig. 1). The question of 2 to 1 block cannot, we believe, be readily answered by a consideration of Figure 1 alone, since it is quite possible that a buried auricular complex may lie in the multiform *R-S* group. However, this difficulty disappears when we consider Figure 2, since the line following the junctional premature beat in Lead II would be broken by an auricular deflection if 2 to 1 block were present; nor will this figure space for 2 to 1 block. The close resemblance between the curves in the two figures is presumptive evidence that the mechanism in each instance is the same.

We believe that the conduction defects, evidenced by prolongation of *P-R* interval (Fig. 1) and by ventricular complexes indicating right branch bundle defect are due to permanent, obstructing lesions in the

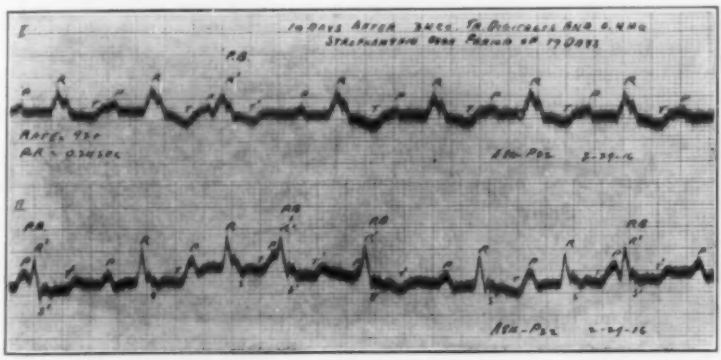
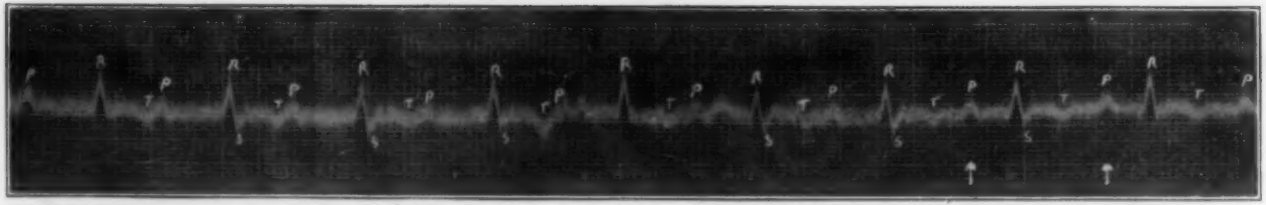


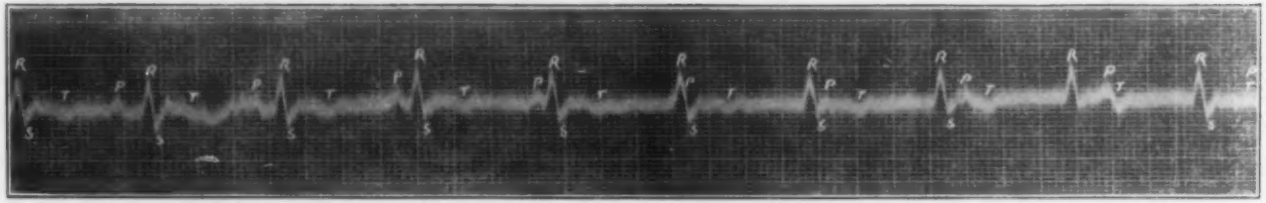
Fig. 14 (Plate 22).—Feb. 29, 1916. Leads I and II show frequent escape of junctional premature beat.

main stem of bundle and in its right branch, since, with minor variations, such defects remained constant during the entire period of observation. In the patient under consideration the etiology of these lesions is obscure. Not only were the usual laboratory tests for syphilis negative, but there was also no clinical or electrocardiographic change while the patient was being given specific treatment.

On the other hand, the periods of complete dissociation (Figs. 4, 5, 8, 11, 12) were transient. In our curves it may be shown that periods of complete dissociation alternated with periods of association (Figs. 4 and 13), and that at times both rhythms appear on a single electrocardiogram (Fig. 13). The cause of dissociation, therefore, must have been either intermittent in action or varying in intensity. The fact that conduction defects, amounting even to complete disso-



Part 1



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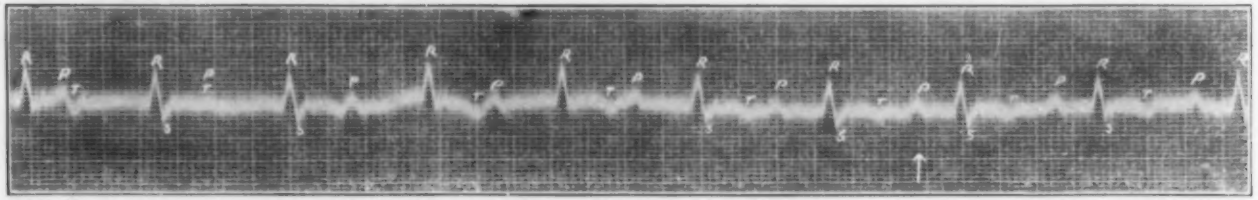

Part 3

Fig. 15 (Bromid Strip 6).—Feb. 13, 1916. Lead II; *A* rate 80, *V* rate 83.3; complete dissociation with apparent resumption of control of both chambers of the heart by the sinus node over two periods of two cycles each (indicated by arrows). *P-R* interval during what appears to be sino-auricular rhythm is 0.28 of a second. A study of many curves shows that this is the usual time interval during periods of association in this case.

Fig. 16 (Plate 6).—Dec. 13, 1915. Type of ventricular complexes seen in Lead III suggesting right preponderance.

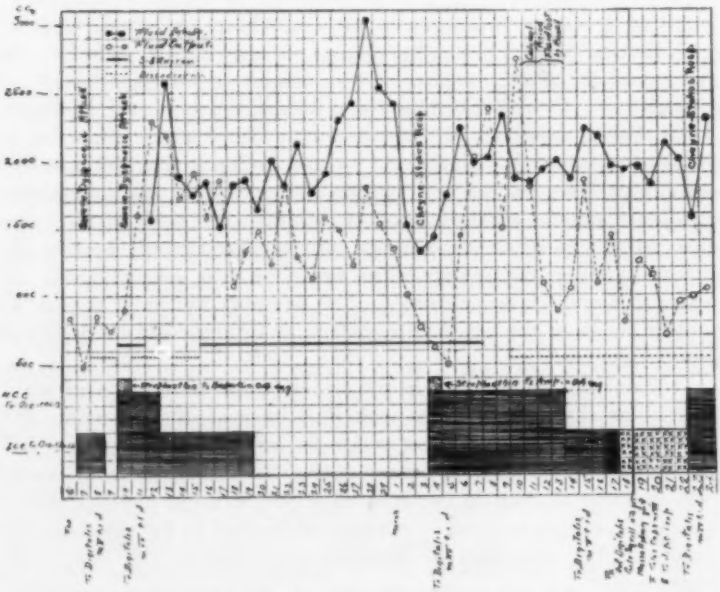

Fig. 17.—The irregular solid line indicates the fluid intake. The irregular dotted line indicates the fluid output. The solid straight line indicates the periods of sino-auricular rhythm. The dotted straight line shows the periods of complete dissociation. The various digitalis preparations administered are indicated by the blocks at the bottom of the chart. The marked decrease in fluid output on March 12, 13 and 14 is associated with the period of free catharsis.

ciation, may arise as a result of disturbance of function and in the absence of permanent obstructive lesions of the bundle we believe to be now well established. Proof of this is based on experimental and clinical evidence. Thus, Lewis, White and Meakins[1] have been able to produce functional heart block in the cat by means of asphyxia. This effect was observed when the heart was responding to sino-auricular rhythm, resulting in forward heart block, or when responding to atrioventricular rhythm, resulting in reversed or backward heart block. Such functional block, it was found, might be produced, intensified and usually relieved at will by regulating the degree of asphyxia to which the tissues were subjected.

Transient complete dissociation may be produced in the mammalian heart by the administration of digitalis. This type of dissociation is often characterized by a ventricular rate which may equal or even exceed the auricular rate. Cushny[2] notes this condition as a manifestation of frequent occurrence in the dog's heart in a toxic state of digitalization. Hewlett and Barringer,[3] writing in 1909, state that the demonstration of this phenomenon is routine in the departments of physiology of Cornell University and of the University of Michigan. As to clinical evidence, not only do they instance a case occurring in the human subject, but Christian,[4] writing in September, 1915, reports two cases (Cases 1 and 2) of transient auriculoventricular dissociation, associated with the administration of digitalis. In Case 1 of this series dissociation appeared after a period of administration of digitalis, disappeared durng the period when the drug was discontinued, and reappeared when it was resumed. "At necropsy the heart showed no evident lesion of the conducting system, and during life blocking had been transitory."

Wilson[5] has shown that in the experimental production of atrioventricular rhythm (of types with *P-R* interval of zero or an *R-P* interval) in the human subject under the influence of atropin, a variable period of dissociation occurs during the transition from normal sino-auricular rhythm to the induced atrioventricular rhythm, during which the auricles respond to impulses elaborated in the sino-auricular node and the ventricles to impulses generated in the *A-V* node.

1. Lewis, T., White, P. D., and Meakins, John: The Susceptible Region in *A-V* Conduction, Heart, 1914, v, 289.
2. Cushny, A. R.: Action of Digitalis Series on Circulation in Mammals, Jour. Exper. Med., 1897, ii, 281.
3. Hewlett, A. W., and Barringer, T. B.: The Effect of Digitalis on the Ventricular Rate in Man, THE ARCHIVES INT. MED., 1910, v, 93.
4. Christian, H. A.: Transient Auriculoventricular Dissociation with Varying Ventricular Complexes Caused by Digitalis, THE ARCHIVES INT. MED., 1915, xvi, 341.
5. Wilson, F. N.: Regular Ectopic Rhythms, Jour. Lab. and Clin. Med., 1916, i, 481.

Although this condition may not be regarded as a functional heart block in the strict interpretation of the term, it is, nevertheless, an instance in which, for transient periods of greater or less duration, there is an independent activity of auricles and ventricles. Lewis, White and Meakins mention epinephrin and anaphylaxis as causative agents in the production of transient complete heart block. It is also occasionally a complication or sequela of the various infections. It is to be observed that the above factors are all transitory in action and that the dissociation which they induce is not permanent.

The relatively rapid rate of the ventricles (Figs. 5 to 8) in our dissociation curves is of especial interest in view of the rarity of such finding in the reported cases of complete dissociation. It is a well-established fact that the rate of impulse formation of experimental bundle lesions is about 30. This is the rate of homogenetic impulse formation in centers below the seat of such lesions, and is the rate of ventricles observed in the majority of cases of clinical dissociation. However, the ventricles may respond to impulses which are furnished by centers having a higher rate of stimulus production than those in the lower portions of the conducting tissues. It has been shown that the automatic rate in ventricular rhythms under the control of the *A-V* node, while lower than that in which the rate is inaugurated by the sino-auricular node, is, nevertheless, higher than the rate in the usual clinical complete heart block, where the centers which lie at the lower levels of the conducting tissue are in control. But in our case the rate of the ventricle is always in excess of the rate of the auricle during the earlier period of observation (Figs. 5 to 8). Presupposing that this rate of ventricle is governed by *A-V* node, or junctional tissues, while the auricle is paced by the sino-auricular node, we find ourselves under the necessity of accounting for this inverted ratio of frequency in impulse formation between the two automatic centers. The solution is suggested by White,[6] who says that "a rapid rhythm arising in atrioventricular junctional tissues, as in some cases of paroxysmal tachycardia, is possibly due to irritation, and not to normal rate of stimulus production in this area of the heart." With this opinion we agree, believing that in this manner, and because of the high location in *A-V* conducting tissues of the site of impulse formation, the rapid ventricular rhythm is produced. We are strengthened in this belief by the proof afforded by our own curves of the exhibition of a high degree of automaticity in these centers. This is evidenced by the frequent escape of premature contractions of junctional origin (Figs. 7 and 14) at a time when the ventricles were otherwise under domination by the sino-auricular node. Such increase in automaticity,

6. White, P. D.: The Archives Int. Med., 1915, xvi, 518.

if the stimulus production is at a rate in excess of that of physiologic stimulus production or approximating it, we believe, may result in the shifting of the function of pacemaker for the ventricles from the sino-auricular node to some portion of the junctional tissue or the *A-V* node, while the auricles continue to respond to impulses originated at the normal site.

We believe that our dissociation curves are illustrative of such mechanism and that two pacemakers coexist, each of which is dominant for the chambers with which it is in closest physiologic connection. The auricles respond to impulses elaborated at approximately the normal rate in the sino-auricular node, and the ventricles to impulses originated at some point high in the *A-V* conducting tissues, which possess a relatively high rate of automaticity.

In addition, it was observed in three instances on our dissociation curves, where the time relationship of *P* and *R* approximated the normal (in this case 0.28 of a second in Lead II), that the sino-auricular rhythm appeared to become temporarily dominant for the whole heart for a period of two complete cycles (Figs. 4 and 15). During the latter period of the study of this case, while the patient was under rather intensive digitalis therapy, the auricular rate was uniformly higher than the ventricular (Figs. 11 and 12), the rates gradually diverging toward the end of the time of our observation. Several factors are probably concerned in the production of this change. It is probably, in part, a manifestation of the usual effect of digitalis. (It is interesting to observe that whenever the effect of this drug became obvious it appeared to have been more pronounced in its action on the ventricular than on the auricular rate.) We must also bear in mind that the patient had undergone a long rest in bed, a fact which may have had something to do with permitting the subsidence of the irritation which we believe to have been present in *A-V* conduction tissues. Finally, it is possible that there had occurred a shifting of pacemaker to a lower level of conducting tissues, with a resulting rate more closely approaching that of ordinary idioventricular rhythm. On no occasion after the establishment of a ventricular rhythm slower than that of the auricle do our records show any evidence of the return of the heart to the sino-auricular rhythm, shown during periods when ventricular rate actually exceeded that of auricular. It would appear that with the divergence of rhythmicity of the two pacemakers there was a decreasing tendency for the sinus node to resume its physiologic function for the whole heart.

Form of Ventricular Complexes.—On several occasions in recent literature there have been references to variations in the form of ventricular complex. Such changes, in general, have been modifications

of ventricular form suggesting preponderant action of one side of the heart over that of the other. Cohn[7] and others[4] suggest that these variations arise as a result of temporary impassability of the conducting tissues, first of one part and then of another. It is thought that such impassability may arise in some instances as a result of the action of digitalis or of other toxic agents.

In our case the changes in contour of ventricular complexes occurred both while the patient was definitely under the influence of digitalis and also at times when such influence was not apparent. These changes occurred while the heart was responding to sino-auricular rhythm and also during periods of complete dissociation. They were most marked in the ventricular complexes of Leads II and III. The usual complex suggested the type associated with left preponderance (Figs. 1 to 5). On some days the contour of ventricular complexes, especially in Lead III, was of the type associated with right preponderance (Fig. 16). At other times there were isolated or grouped instances of alteration from one form to the other in the same lead (Fig. 8). Many changes of form intermediate between them were observed.

Digitalis effects, as expressed by alteration in contour of *T* wave,[8] or in prolongation of *P-R* interval,[9] were not apparent in our case, though a series of about thirty electrocardiograms taken during digitalis administration was examined for such changes. We have no doubt that this is because the reaction of a definitely damaged heart to this drug can scarcely be compared with the reaction of apparently normal hearts. During the last period of digitalis therapy a marked ventricular arrhythmia (Fig. 12) occurred at a time when the heart was in dissociation. We believe this to be a manifestation of the action of digitalis.[2]

The clinical results of digitalis therapy in regard to this patient were always favorable, sometimes strikingly so. The effect on fluid output is shown in Figure 17, for which we are indebted to Dr. J. C. Baldwin. In the period of discontinuance of digitalis, during the midperiod of second admission, heart failure became progressively more marked; the resumption of digitalis was followed by a correspondingly marked improvement in the circulation. This observation is of especial

7. Cohn, A. E.: The Present Status of the Electrocardiographic Method in Clinical Medicine, Am. Jour. Med. Sc., 1916, cli, 541; A Case of Transient Complete Auriculoventricular Dissociation, showing Constantly Varying Ventricular Complexes, Heart, 1913, v, 5.

8. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: The Effect of Digitalis on the *T* Wave of the Normal Human Electrocardiogram, Jour. Exper. Med., 1915, xxi, 593.

9. White, P. D., and Sattler, R. R.: The Effect of Digitalis on the Normal Human Electrocardiogram, with Especial Reference to *A-V* Conduction, Jour. Exper. Med., 1916, xxiii, 613.

interest in view of the existence of a distinct theoretical contraindication for the use of digitalis in this case. A record of the digitalis administration during the entire period of observation is shown in the table.

TABLE OF DIGITALIS AND ALLIED DRUGS ADMINISTERED

Date 11/13/15	Preparation Tr. Digitalis	Daily Doses 1 c.c.	Total Doses 3 c.c.
First admission			
11/16/15	None		
11/16/15 to 2/2/16	None		
2/ 3/16	Tr. Digitalis	1 c.c.	
2/ 4/16	Tr. Digitalis	2.33 c.c.	
2/ 5/16	Tr. Digitalis	0.67 c.c.	4 c.c.
Second admission	None		
2/ 7/16	Tr. Digitalis	2 c.c.	
2/ 8/16	Tr. Digitalis	2 c.c.	4 c.c.
2/10/16	Strophanthin (intravenous)	0.4 mg.	0.4 mg.
2/10-13/16	Tr. Digitalis	4 c.c.	12 c.c.
2/13-19/16	Tr. Digitalis	2 c.c.	14 c.c.
3/3/16	Strophanthin (intravenous)	0.4 mg.	0.4 mg.
3/ 3-14/16	Tr. Digitalis	4 c.c.	40 c.c.
3/14-18/16	Tr. Digitalis	2 c.c.	8 c.c.
3/18-22/16	Pow'd digitalis	0.2 gm.	1 gm.
	Powdered squills	0.2 gm.	1 gm.
3/23-25/16	Tr. Digitalis	4 c.c.	12 c.c.

SUMMARY

A case is reported in which a sino-auricular rhythm of the whole heart is interrupted by periods of total dissociation of auricles and ventricles. During all but one of these periods the rate of the ventricles exceeded that of the auricles. This type of rhythm is highly suggestive of digitalis poisoning. It is admitted that digitalis effect could not have been absolutely excluded at any time while our patient remained under observation. Nevertheless, because we take into account the fact that the first onset of dissociation was observed twenty-eight days after the ingestion of 3 c.c. of tincture of digitalis, extending over a period of three days, we believe that the connection between the administration of digitalis and dissociation is problematic. On the other hand, a positive effect of digitalis administration may be noted in the marked clinical improvement which occurred more than once in a patient in whom stem and branch bundle defect would have been regarded under ordinary circumstances as a contraindication to the use of the drug.

EXPERIMENTS ON THE ORIGIN AND CONDUCTION OF THE CARDIAC IMPULSE

VI. CONDUCTION OF THE EXCITATION FROM THE SINO-AURICULAR NODE TO THE RIGHT AURICLE AND AURICULOVENTRICULAR NODE *

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INTRODUCTION

The experiments to be described in this paper were undertaken in an attempt to determine the normal path or paths of conduction of the cardiac impulse from its origin in the upper part of the sino-auricular node to the right auricle and to the auriculoventricular node. The problem was attacked in two ways: first, by an attempt to map out the path of the spread of electronegativity from the sino-auricular node to surrounding parts in the intact heart; and second, the determination of the influence on conduction from the sino-auricular node to the right auricle and auriculoventricular node produced by a gradual and progressive isolation of the sino-auricular node from the surrounding tissues.

So far as we have been able to find, no previous work has been done in which the sino-auricular node has been gradually isolated from the surrounding tissues in the heart in situ, with the exception of a few experiments of this character reported by us in a preceding paper of this series.[1] Cohn, Kessel and Mason,[2] working on the excised artificially perfused dog's heart, state that such incisions cause merely an increase in rate of the heart. Hering[3] found that a single cut through the sulcus terminalis may cause a transitory stoppage of the supraventricular regions, a result not confirmed by subsequent workers.

METHODS

The experiments were all performed on dogs. The animals were given a preliminary injection of morphin, etherized and the thorax opened under artificial respiration with air warmed to body temperature. An extensive exposure of the right auricle and intercaval regions was obtained by opening the thorax well down on the right side and rotating the heart slightly to the left, in which position it was held by

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* From the Physiological Laboratory of the University of Wisconsin.
1. Meek and Eyster: Heart, 1914, v, 227.
2. Cohn, Kessel and Mason: Heart, 1911-1912, iii, 311, 341.
3. Hering: Arch. f. d. ges. Physiol., 1910, cxxxvi, 466.

ligatures attached to the auriculoventricular border. Systoles of the right auricle and right ventricle were recorded by suspension and air transmission to ambours writing on a Hürthle kymographion or recording on bromid paper in a photographic registration apparatus. In addition, galvanometric records of one type or another were made in all experiments except four (Experiments 11, 12, 15 and 16). The large electromagnetic thread galvanometer of Edelmann was used for this purpose. These records were made always for one of two purposes, either to determine the seat of the pacemaker and to trace the course of the wave of negativity by determining the sequence of negativity at certain selected points, or to determine the time relation of onset of negativity in any two or more points. The first method depends on the fact that if the direction of movement of the galvanometer fiber, when one of the terminals becomes electronegative to the other, is determined beforehand, it is possible to find which one of any two points shows the initial change in this respect. By selecting a number of points on the surface of the heart it is possible by comparing each one of these with every other one to determine the sequence of negativity in these various regions. For reasons which we have previously discussed,[4] we do not regard this method, however, as suitable for the accurate determination of the time intervals of the occurrence of negativity in different regions. To determine this we have used two other methods, the first of which we have already described.[4] This consists in a determination of the difference in time between the occurrence of the initial electrical change at any two points and the onset of mechanical systole of the auricle as recorded by the suspension curve. If the negativity in point *a* precedes the mechanical systole by an interval of time represented by *x*, and point *b* by an interval of time represented by *y*, the time from the appearance of negativity in *a* to that in *b* would be given by $x - y$. This method of measuring the rate of propagation was used in five experiments reported in this paper (Experiments 32 to 36, inclusive). There are two disadvantages connected with this method: first, the difficulty of determining on a record taken at fast speed, when dealing with small intervals of time, the exact onset of the mechanical systole; and second, the fact that determinations are not made within the same heart beat, but involve comparisons between different cycles. The latter we minimized by devising a key which allowed rapid change of connections, so that comparisons between the galvanometer curves from a number of different points and the suspension curve could be made over a minimal number of heart cycles. The second method for determining the time interval of negativity between two points consists in using two

4. Eyster and Meek: Heart, 1914, v, 119.

separate circuits to two galvanometers, a pair of electrodes placed close together[5] being applied to each region and connected to one of the galvanometers, the other point carrying two electrodes connected similarly to the other galvanometer. The difference in time of onset of the two curves is a measure of the time relation of the onset of the electrical change in the two regions. The records in all cases were made on bromid paper moving usually at a speed such that the marks of a tuning fork vibrating 100 times per second were spaced from 2 to 4 mm. apart. Since the onset of such curves is nearly always very sharp, accurate time measurements with an error less than 0.0025 of a second were possible.

The electrodes used were of the zinc and zinc sulphate type. When applied to the surface of the heart, the terminal was composed of a piece of woolen yarn saturated with salt solution and attached to the epicardium with a light silk ligature. For application to the auricular portion of the auriculoventricular node (coronary sinus[6]) a curved electrode terminating in a soft pad of macerated filter paper was applied to the region of the mouth of the coronary vein on the external surface of the auricle. For application to the ventricular portion of the auriculoventricular node, a similar electrode, but longer and curved near the tip, was passed down through the right external jugular vein and superior vena cava until its end was in contact with the interauricular septum in the region over the node. The position of this electrode was confirmed by examination after the experiment was terminated. When two galvanometers were used for determining the time interval of the electrical change, a pair of electrodes cemented together were applied as above.

In those experiments in which the region of the sino-auricular node was gradually isolated and the influence on the seat of impulse formation and on conduction studied, interruption of the physiologic continuity of the tissues was secured by ligating, clamping, or cutting. Ligation was only employed when the span of tissue included was short and serious distortion of neighboring parts was not produced. In all cases in which the extent of the region to be interrupted was greater, clamping or cutting was employed. When it was desired that the interruption be permanent, the tissue was cut. Clamping, on the other hand, was resorted to when the results of gradual or temporary interruption of the functional continuity were desired. The clamp used was

5. We here found this more satisfactory in practice than the employment of the so-called differential electrode of Clements (Ztschr., 1912, lviii, 110). In this a single bent thread connected with two electrodes is applied to the heart. The decrease in the electrical potential difference by this procedure may tend to cause the loss of a small initial change and the comparative looseness of the galvanometer fiber required results in slower reactivity.

6. Aschoff: Centralbl. f. allg. Path. u path. Anat., 1910, xxi, 433.

one devised for the purpose and consisted of a holder through which a straight needle could be passed and uniform pressure made on it. The method of making cuts in the heart beating in situ has been described in a previous paper of this series.[1]

EXPERIMENTS IN WHICH THE PATH OF CONDUCTION WAS STUDIED BY MEANS OF COMPARISONS OF ONSET OF NEGATIVITY IN VARIOUS ELECTRODES

Experiments somewhat similar to the experiments performed in this series have been previously reported by ourselves[4] and more recently by Lewis.[7] In our previous work we found a radial spread of the excitation from the node, with a tendency, however, to a more rapid spread of the negativity to the intercaval or venous side of the

TABLE 1.—SEQUENCE OF NEGATIVITY OF THE POINTS SHOWN IN FIGURE 1 *

Experiment	Sequence of Negativity								
1	2	4	3	1	6	7	5	8	9
2	1	4	3	5	7	9 †			
3	1	3	5	4	7	9 †			
4	1	3	5	4	9	7 †			

* In each experiment head of Sa node was shown to be negative to all other points and to Av node.
† Points 2, 6 and 8 were not determined in these experiments.

TABLE 2.—SEQUENCE OF NEGATIVITY OF THE POINTS SHOWN IN FIGURE 2

Experiment	Sequence of Negativity											
5	1	2	8	5	4	3	6	9	7	12	11	10
6	2	1	4	3	5	6	9	10	12	11	7	8
7	3	1	2	7	4	8	5	10	11	12	6	9
8	1	2	3	5	6	9	7	4	10	11	8	12
9	2	1	4	3	7	5	6	10	11	9	8	12
10	1	4	2	3	5	7	6	8	9	10	12	11

sino-auricular node than to the auricular side, since points on the former equidistant from the node usually show negativity before points on the right auricle. Lewis is content to state that the excitation spreads radially in all directions from the node. The experiments which we have more recently undertaken were planned with the purpose to study this matter in greater detail and to find, if possible, whether some part of this radial path conducts the excitation more rapidly than all other parts. Ten experiments of this character were

7. Lewis: In Harvey Lectures, 1914-1915, x, 60.

carried out. In four a single circle of points as nearly as possible equidistant from and surrounding the sino-auricular node were compared. Each point was compared with every other point, so that the sequence of negativity could be obtained. To be sure that we were dealing with a normal sino-auricular rhythm, the upper end of the sino-auricular node was also compared with all of these points and with the auriculoventricular node. The disposition of the points compared is shown in Figure 1. The numbers in this figure refer to Table 1, which gives the sequence of negativity of these points in the four experiments. Figure 2 and Table 2 give the corresponding data for the remaining six experiments, in which two circles of points were compared in a similar way to the above.

Fig. 1 Fig. 2 Fig. 3

Fig. 1.—Four points along auricle and four points in intercaval region, each pair equidistant from the head of the *Sa* node, compared as to onset of negativity. In addition, comparisons were made between the *Sa* node and the point above the node near the auricular septum (point 4), the same distance from the node as the points on the auricular and the venous side.

Fig. 2.—Point 8 is in a similar position to point 4 of the preceding experiments. Point 9 is on the ventricular portion of the auriculoventricular node.

Fig. 3.—Position and designation of interruptions made around the sino-auricular node.

EXPERIMENTS IN WHICH THERE WAS PARTIAL OR COMPLETE ISOLATION OF THE SINO-AURICULAR NODE

Interruption of the physiologic continuity of the tissues on one or more of the four sides of the sino-auricular node was secured by ligating, clamping or cutting, as previously described. The position of the interruptions is noted in the tables as follows: (1) across the sulcus terminalis, at right angles to the long axis of the sino-auricular node and from 5 to 10 mm. below this structure; (2) along the intercaval or venous border of the sulcus, beginning at the venous end of (1) and ending opposite a point a few millimeters above the head of the node; (3) across the junction of the superior vena cava and

appendage of the right auricle, a few millimeters above the head of the node; (4) along the auricular border of the sulcus, joining the auricular ends of (1) and (3) (Fig. 3). In the summaries in the table no statement is made as to the method of interruption, since the different methods used gave identical results. Interruptions 1 and 3 were frequently but by no means always made by ligation; 2 and 4 always by cutting or clamping, except in a few cases in which multiple ligatures were employed. The series of four interruptions, when complete,

TABLE 3.—Record of Contractions of Right Auricle and Right Ventricle

Experiment	Procedure	As-Vs, Sec.	Cycle, Sec.	Pacemaker
11	Normal	0.100	0.370	Sa
	Cut 4	0.100	0.410	Sa
12	Normal	0.090	0.350	Sa
	Cut 3	0.090	0.350	Sa
	Cut 1	0.080	0.470	Av
13	Normal	0.120	0.340	Sa
	Cut 4	0.12	0.34	Sa
	Cut 3	0.12	0.34	Sa
	Cut 2	0.08	0.62	Av†
14	Normal	0.13	0.40	Sa
	Cut 4	0.11	0.43	Sa
	Cut 2	0.06	0.45	C.S†
15	Normal	0.10	0.36	Sa
	Cut 4	0.10	0.36	Sa
	Cut 3	0.10	0.40	Sa
	Cut 1	0.06	0.40	Sa
	Cut 2	0.00	0.50	Av
16	Normal	0.18	0.69	Sa
	Cut 4	0.18	0.51	Sa
	Cut 1	0.18	0.57	Sa
	Cut 3	0.18	0.57	Sa
	Cut 2	0.08	0.90	Av
17	Normal	0.17	0.33	Sa
	Cut 4	0.15	0.38	Sa
	Cut 1	0.11	0.40	Sa†
	Cut 3	0.11	0.40	Sa†
	Cut 2	0.05	0.48	Av†
18	Normal	0.12	0.42	Sa
	Cut 4	0.09	0.40	Sa
	Cut 3	0.02*	0.60	Av†
19	Normal	0.11	0.35	Sa†
	Cut 4	0.12	0.40	Sa†
	Cut 2	0.12	0.40	Sa†
	Cut 3	0.10	0.47	Sa†
	Cut 1	0.06	0.62	C.S†

* To be read Vs-As instead of As-Vs.
† Position of pacemaker confirmed by comparisons of onset of negativity with galvanometer.

entirely surround and isolate the sino-auricular node from the remainder of the heart. Considerable histologic experience has indicated to us the rather marked constancy of the position and extent of the sino-auricular node in the dog's heart, and sufficient margin was given when carrying out the isolation of the node to avoid implication of this structure in the lesions produced. The area isolated included, therefore, in addition to the sino-auricular node a margin

varying from two to three millimeters in width of auricular or intercaval tissues surrounding the node.

In Table 3 are summarized the results from nine experiments in which the contractions of the right auricle and right ventricle were

TABLE 4.—COMPARISON OF ONSET OF NEGATIVITY MADE BETWEEN FIVE DIFFERENT POINTS

Experiment	Procedure	Sequence of Negativity
20	Normal	Sa-Svc-Av-Cs-Ra
	Cut 1	Av-Sa-Ra
21	Normal	Sa-Svc-Av-Cs-Ra
	Cut 2	Sa-Svc-Ra-A-Cs
	Cut 1	Sa-Svc-Ra-A-Cs
22	Normal	Sa-Av-Svc-Cs-Ra
	Cut 3	Sa-Svc-Cs-Ra-Av
	Cut 2	Av-Cs-Ra-Svc-Sa
23	Normal	Sa-Svc-Av-Ra-Cs
	Cut 1	Sa-Svc-Ra-Av-Cs
	Cut 2	Av-Cs-Ra-Svc-Sa
	Cut 3	Av-Cs-Svc-Sa-Ra
24	Normal	Sa-Svc-Av-Cs-Ra
	Cut 1	Sa-Av-Svc-Cs-Ra
	Cut 2	Av-Cs-Ra-Sa-Svc
25	Normal	Sa-Svc-Cs-Ra-Av
	Cut 1	Av-Ra-Sa-Cs-Svc
	Cut 2	Av-Ra-Sa-Svc-Cs
	Cut 3	Av-Ra-Sa-Cs-Svc
26	Normal	Sa-Svc-Av-Ra-Cs
	Cut 1	Sa-Svc-Ra-Cs-Av
	Cut 2	Sa-Svc-Ra-Cs-Av
	Cut 3	Sa-Svc-Ra-Cs-Av
	Cut 4*	Sa-Svc-Ra-Cs-Av
27	Normal	Sa-Svc-Av-Cs-Ra
	Cut 1	Sa-Svc-Av-Cs-Ra
	Cut 2	Sa-Svc-Av-Ra-Cs
	Cut 3	Cs-Ra-Av-Svc-Sa
	Cut 4	Cs-Ra-Av-Svc-Sa
28	Normal	Sa-Svc-Ra-Av-Cs
	Cut 1	Sa-Svc-Ra-Av-Cs
	Cut 2	Sa-Svc-Ra-Av-Cs
	Cut 4	Sa-Svc-Av-Ra-Cs
	Cut 3	Av-Cs-Ra-Sa-Svc
29	Normal	Sa-Svc-Ra-Av-Cs
	Cut 1	Sa-Svc-Ra-Av-Cs
	Cut 2	Sa-Svc-Ra-Av-Cs
	Cut 4	Sa-Ra-Svc-Cs-Av
	Cut 3	Cs-Ra-Svc-Av-Sa
30	Normal	Sa-Av-Cs-Ra-Svc
	Cut 1	Sa-Ra-Av-Cs-Svc
	Cut 2	Av-Cs-Sa-Ra-Svc
31	Normal	Sa-Svc-Av-Ra-Cs
	Cut 4	Sa-Svc-Av-Ra-Cs
	Cut 2	Av-Ra-Sa-Svc-Cs
	Cut 1	Av-Ra-Cs-Sa-Svc

* Cut 4 was incomplete, about 8 mm. at the upper portion being open.

recorded and the sino-auricular node partially or completely isolated. Galvanometer records were made only in those instances in which the length of the *As-Vs* interval did not point to the position of the pace-

maker or when it seemed desirable to confirm this position by another method. The use of the galvanometer in these experiments was confined to comparisons of the onset of negativity between the sino-auricular node, right auricle, coronary series and ventricular portion of the auriculoventricular node. No attempt was made to measure the normal interval of onset of negativity between these regions or the influence on this of the interruption of the connections of the node.

In Table 4 are summarized the results from twelve experiments, in which comparisons of the onset of negativity were made between five different points on the heart, before and after partial or complete isolation of the sino-auricular node. The five points were (1) the upper portion of the sino-auricular node (*Sa*), (2) the mouth of the superior vena cava a few millimeters above its junction with the right auricle (*S.v.c.*), (3) the body of the right auricle (*Ra*), (4) the auricular portion of the auriculoventricular node (coronary sinus, *Cs*) and (5) the ventricular portion of the same node (*Av*). These were compared in couples, the direction of movement of the galvanometer fiber in each case indicating which one of the two points manifested initial negativity. Mechanical systole of the right auricle was also recorded by means of air transmission to a tambour, the lever of which moved in front of the slit of the photographic registration apparatus. A specially devised contact key connected the different electrodes in such a way that any two could be connected through the galvanometer and rapid change made from one couple to another. A complete series of comparisons between all five points could in this way be made over a very short period of time. The interruptions of the tissues around the node are numbered as in the previous table and as indicated in Figure 3.

In Table 5 are summarized the results from thirty-five experiments in which measurements of the intervals of the onset of negativity were made between (1) the sino-auricular node and the ventricular portion of the auriculoventricular node (*Sa-Av*), (2) the sino-auricular node and the body of the right auricle (*Sa-Ra*), and (3) between the ventricular portion of the auriculoventricular node and right auricle (*Av-Ra*). The mechanical systoles of the right auricle and right ventricle were also recorded by air transmission by means of tambours before the slit of the photographic registration apparatus. In many of these experiments records of auricular and ventricular systoles were also made on a Hürthle kymographion, in order to allow measurement of auriculoventricular intervals (*As-Vs*) during the course of the experiments. In certain cases, as noted in the table, the position of the pacemaker was confirmed by direct comparisons of negativity between electrodes placed as in the preceding group of experiments, summarized in Table 4. Determination of the conduction

TABLE 5.—Summary of Results of Thirty-Five Experiments Measuring Intervals of Onset of Negativity Between Different Parts of Heart

Experiment	Procedure	Sa-Av, Sec.	Av-Sa, Sec.	Sa-Ra, Sec.	Av-Ra, Sec.	Ra-Av, Sec.	As-Vs, Sec.	Cycle, Sec.	Pacemaker
32	Normal	0.030	.....	0.025	.....	0.005	0.140	0.550	Sa
	Cut 4	0.045	.....	0.030	.....	0.015	0.120	0.580	Sa
	Cut 1	0.000	.....	.....	.....	.....	0.040	0.700	C.S.
33	Normal	0.025	.....	0.025	.....	0.000	0.090	0.350	Sa
	Cut 2	0.050	.....	0.023	.....	0.027	0.080	0.380	Sa
	Cut 3	.....	0.010	.....	0.015	.....	0.000	0.470	Av
34	Normal	0.040	.....	0.030	.....	0.010	0.097	0.375	Sa
	Cut 3	0.055	.....	0.025	.....	0.030	0.095	0.400	Sa
	Cut 2	0.055	.....	0.025	.....	0.030	0.090	0.480	Sa
	Cut 4	.....	0.020	0.005	0.025	.....	0.000	0.640	Av
35	Normal	0.030	.....	0.030	.....	0.000	0.115	0.047	Sa
	Cut 4	0.030	.....	0.055	0.025	.....	0.110	0.053	Sa
	Cut 1	.....	0.010	0.040	0.050	.....	0.060	0.110	Av
36	Normal	0.035	.....	0.035	.....	0.000	0.110	0.330	Sa
	Cut 4	.....	.....	0.045	.....	.....	0.105	0.330	Sa
	Cut 3	.....	0.025	0.015	0.040	.....	0.060	0.460	Av
37	Normal	.....	0.028	0.014	0.042	.....	.....	.....	Av
	Cut 4	.....	.....	.....	0.044	.....	.....	.....	Av
38	Normal	0.048	.....	0.028	.....	0.020	.....	.....	Sa
	Cut 4	.....	0.020	0.005	.....	.....	.....	.....	Av*
39	Normal	0.070	.....	0.025	0.005	.....	.....	0.350	Sa
	Cut 4	0.013	.....	0.053	0.040	.....	.....	0.350	Sa
	Cut 3	0.007	.....	0.007	.....	.....	.....	0.450	?
	Cut 1	.....	0.023	0.018**	0.005	.....	.....	0.460	Av
40	Normal	0.028	.....	0.020	.....	0.008	0.080	0.440	Sa
	Cut 2	.....	0.010	0.013	0.023	.....	0.000	0.650	Av
41	Normal	0.024	.....	0.020	.....	0.004	0.100	0.360	Sa
	Cut 2	.....	0.005	0.003	0.002	.....	0.075	0.430	C.S.
42	Normal	0.022	.....	0.030	0.008	.....	0.070	0.410	Sa
	Cut 4	0.016	.....	0.035	0.019	.....	0.070	0.410	Sa
	Cut 1	.....	.....	.....	.....	.....	0.070	0.600	Av†
43	Normal	0.007	.....	0.012	0.005	.....	0.105	0.420	Sa
	Cut 1	0.015	.....	0.015	0.000	.....	0.090	0.420	Sa
	Cut 2	0.017	.....	0.011	.....	0.006	0.090	0.430	Sa
44	Normal	0.007	.....	0.018	0.011	.....	0.110	0.420	Sa
	Cut 1	.....	0.021	0.009**	0.012	.....	0.045	0.545	Av
	Later	.....	.....	.....	.....	.....	0.090	0.480	Sa†
	Cut 2	0.000	.....	0.000	0.000	.....	0.100	0.500	C.S.†
45	Normal	0.032	.....	0.020	.....	0.012	0.130	0.350	Sa
	Cut 1	0.043	.....	0.015	.....	0.028	0.140	0.410	Sa
	Cut 2	0.046	.....	0.010	.....	0.036	0.110	0.500	Sa
46	Normal	0.021	.....	0.016	.....	0.005	0.110	0.350	Sa
	Cut 1	0.025	.....	0.012	.....	0.013	0.110	0.370	Sa
	Later	.....	.....	0.013	.....	.....	0.000	0.420	Av
	Later	.....	.....	.....	.....	.....	0.110	0.410	Sa†
	Cut 2	0.032	.....	0.013	.....	0.019	0.110	0.430	Sa
47	Normal	0.020	.....	0.013	.....	0.007	0.110	0.430	Sa
	Cut 1	.....	.....	.....	.....	.....	0.000	.....	Av
	Later	0.036	.....	0.016	.....	0.020	0.165	0.310	Sa
	Cut 2	0.037	.....	0.015	.....	0.022	0.160	0.460	Sa†
48	Normal	0.028	.....	0.016	.....	0.012	0.095	0.350	Sa
	Cut 1	0.024	.....	.....	.....	.....	0.070	0.365	Sa‡
	Later	0.033	.....	0.016	.....	0.017	0.070	0.350	Sa
	Cut 2	.....	0.016	.....	.....	.....	0.030	0.450	Av
	Later	0.040	.....	0.020	.....	0.020	0.070	0.410	Sa

TABLE 5.—Summary of Results of Thirty-Five Experiments Measuring Intervals of Onset of Negativity Between Different Parts of Heart—(*Continued*)

Experiment	Procedure	Sa-Av, Sec.	Av-Sa, Sec.	Sa-Ra, Sec.	Av-Ra, Sec.	Ra-Av, Sec.	As-Vs, Sec.	Cycle, Sec.	Pacemaker
49	Normal	0.012	.....	0.017	0.005	.....	0.080	0.230	Sa
	Cut 1	0.005	.....	.....	.....	.....	0.100	0.310	?
	Later	0.023	.....	.....	.....	.....	0.100	0.350	Sa
	Cut 2	.....	0.008	0.007	0.015	.....	0.060	0.375	Av
	Later	0.033	.....	.....	.....	.....	0.080	0.380	Sa
50	Normal	0.026	.....	0.011	.....	0.015	0.100	0.350	Sa
	Cut 2	0.007	.....	.....	.....	.....	0.060	0.420	?
	Cut 1	.....	0.025	0.000	.....	.....	0.040	0.480	Av†
51	Normal	.....	0.016	.....	.....	.....	0.060	0.380	Av
	Cut 1	.....	0.018	.....	.....	.....	0.060	0.380	Av
	Cut 2	.....	0.043	.....	.....	.....	0.040	0.370	Av
52	Normal	0.020	.....	.....	.....	.....	0.120	0.270	Sa
	Cut 2	0.030	.....	.....	.....	.....	0.120	0.270	Sa
	Cut 1	0.035	.....	.....	.....	.....	0.120	0.280	Sa
	Cut 3	.....	0.003	.....	.....	.....	0.080	0.320	Av†
53	Normal	0.026	.....	0.020	.....	0.006	0.100	0.420	Sa
	Cut 4	0.026	.....	0.026	.....	0.000	0.100	0.460	Sa
	Cut 1	0.026	.....	0.026	.....	0.000	0.100	0.520	Sa
	Cut 2	.....	0.022	.....	.....	.....	0.000	0.680	Av
54	Normal	0.022	.....	0.013	.....	0.009	0.080	0.290	Sa
	Cut 4	0.017	.....	0.009	0.008	.....	0.120	0.320	Sa
	Cut 2	.....	0.026	0.000	0.026	.....	0.080¶	0.400	Av
55	Normal	0.030	.....	0.014	.....	0.016	0.100	0.420	Sa
	Cut 4	0.030	.....	0.028	.....	0.002	0.100	0.430	Sa
	Cut 2	0.000	.....	0.000	.....	.....	0.060	0.490	C.S.
	Cut 1	.....	0.019	0.016**	0.003	.....	0.060	0.490	Av
56	Normal	0.024	.....	0.016	.....	0.008	0.120	0.300	Sa
	Cut 2	0.024	.....	0.016	.....	0.008	0.120	0.270	Sa
	Cut 3	0.024	.....	0.014	.....	0.010	0.110	0.320	Sa
	Cut 1	.....	0.31	0.007	0.38	.....	0.000	0.370	Av
57	Normal	0.035	.....	0.030	.....	0.005	0.140	0.290	Sa
	Cut 2§	.....	0.003	.....	.....	.....	0.090	0.330	C.S.
	Later	0.035	.....	.....	.....	.....	0.130	0.330	Sa
	Cut 2§	0.035	.....	0.024	.....	0.011	0.125	0.340	Sa
	Cut 1	.....	0.031	0.012	0.047	.....	0.040¶	0.370	Av
58	Normal	0.027	.....	0.040	0.013	.....	0.220	0.400	Sa
	Cut 3	0.027	.....	.....	.....	.....	0.220	0.500	Sa
	Cut 1	0.000	.....	.....	.....	.....	0.190	0.560	C.S.†
	Cut 2	0.000	.....	.....	.....	.....	0.180	0.540	C.S.
	Cut 4	.....	0.010	.....	.....	.....	0.120	1.000	Av
59	Normal	0.025	.....	.....	.....	.....	0.100	0.410	Sa
	Cut 3	0.040	.....	.....	.....	.....	0.130	0.410	Sa
	Cut 1	0.040	.....	.....	.....	.....	0.100	0.380	Sa
	Cut 2	.....	0.027	.....	.....	.....	0.045	0.430	Av
	Cut 4	.....	0.027	.....	.....	.....	0.045	0.430	Av
60	Normal	0.012	.....	.....	.....	.....	0.097	0.370	Sa
	Cut 3	.....	0.005	.....	.....	.....	0.020	0.400	Av
	Later	0.030	.....	.....	.....	.....	0.080	0.350	Sa
	Cut 1	.....	0.026	.....	.....	.....	0.000	0.390	Av
61	Normal	0.031	.....	.....	.....	.....	0.200	0.350	Sa
	Cut 3	.....	0.069	.....	.....	.....	0.060¶	0.380	Av
	Later	0.060	.....	.....	.....	.....	0.165	0.370	Sa
	Cut 1	0.060	.....	.....	.....	.....	0.130	0.360	Sa
	Cut 2	0.060	.....	.....	.....	.....	0.120	0.400	Sa†
62	Normal	0.013	.....	.....	.....	.....	0.083	0.360	Sa
	Cut 3	.....	0.005	.....	.....	.....	0.027	0.420	Av
	Later	0.016	.....	.....	.....	.....	0.090	0.400	Sa

TABLE 5.—SUMMARY OF RESULTS OF THIRTY-FIVE EXPERIMENTS MEASURING INTERVALS OF ONSET OF NEGATIVITY BETWEEN DIFFERENT PARTS OF HEART—(*Continued*)

Experiment	Procedure	Sa-Av, Sec.	Av-Sa, Sec.	Sa-Ra, Sec.	Av-Ra, Sec.	Ra-Av, Sec.	As-Vs, Sec.	Cycle, Sec.	Pacemaker
63	Normal	0.024	.....	.....	.....	.....	0.100	0.320	Sa
	Cut 3	.....	0.014	.....	.....	.....	0.060	0.350	Av
	Cut 1	.....	0.030	.....	.....	.....	0.060	0.370	Av
	Later	0.054	.....	.....	.....	.....	0.060	0.370	Sa
	Later	.....	0.020	.....	.....	.....	0.060	0.440	Av
64	Normal	0.036	.....	.....	.....	.....	0.160	0.380	Sa
	Cut 3	0.042	.....	.....	.....	.....	0.160	0.370	Sa
	Cut 1	0.043	.....	.....	.....	.....	0.130	0.430	Sa†
	Cut 2	.....	0.019	.....	.....	.....	0.100	0.480	Av
65	Normal	0.022	.....	.....	.....	.....	0.152	0.540	Sa
	Cut 1	0.050	.....	.....	.....	.....	0.190	0.400	Sa
	Later	0.030	.....	.....	.....	.....	0.170	0.500	Sa
	Cut 3	0.045	.....	.....	.....	.....	0.180	0.470	Sa
	Cut 2	.....	0.014	.....	.....	.....	0.130	0.600	Av
	Later	0.030	.....	.....	.....	.....	0.150	0.500	Sa
	Cut 4	.....	.....	.....	.....	.....	0.000	0.600	Av
66	Normal	0.013	.....	.....	.....	.....	0.104	0.240	Sa
	Lig. 1§	0.024	.....	.....	.....	.....	0.100	0.280	Sa
	Lig. 1 relieved	0.018	.....	.....	.....	.....	0.105	0.280	Sa
	Cut 3	0.040	.....	.....	.....	.....	0.110	0.400	Sa
	Later	0.002	.....	.....	.....	.....	0.100	0.400	Sa
	Lig. 1	.....	0.020	.....	.....	.....	0.025	0.500	Av

* Necropsy showed that Cut 4 involved the upper part of the Sa node.
** To be read Ra-Sa instead of Sa-Ra.
† Position noted shown to be seat of pacemaker by comparison of onset of negativity with other regions.
‡ Comparisons of onset of negativity indicated that pacemaker was in lower portion of Sa node.
¶ To be read Vs-As instead of As-Vs.
§ In this experiment, Cut 2 was made in two parts, the upper half first.
# In this experiment Ligature 1 was laid and tied in the usual position of Cut 1. When not otherwise noted, Sa indicates seat of pacemaker in upper part of Sa node.

intervals, as noted above, and of the *As-Vs* interval and length of cycle were made before and after partial or complete isolation of the sino-auricular node. In all cases these determinations represent averages from a number of cycles. The positions of the interruptions surrounding the node are given in Figure 3. In some of these experiments a part of the isolation was carried out by gradual clamping in an attempt to obtain partial sino-auricular or sinoventricular block, and continuous records made with measurements of *Sa-Av* conduction, *As-Vs* interval and length of cycle throughout the whole period of tightening the clamp. The results from this part of the work with other experiments bearing on this problem will be reported in a subsequent paper, and at this time there will be considered only the results on the position of the pacemaker and on the conduction time consequent on complete functional interruption of the clamped tissue.

The rate of conduction of the wave of negativity between the sino-auricular and auriculoventricular nodes and the right auricle was determined in the first five experiments of Table 5 by the procedure first described in the discussion under methods. One galvanometer

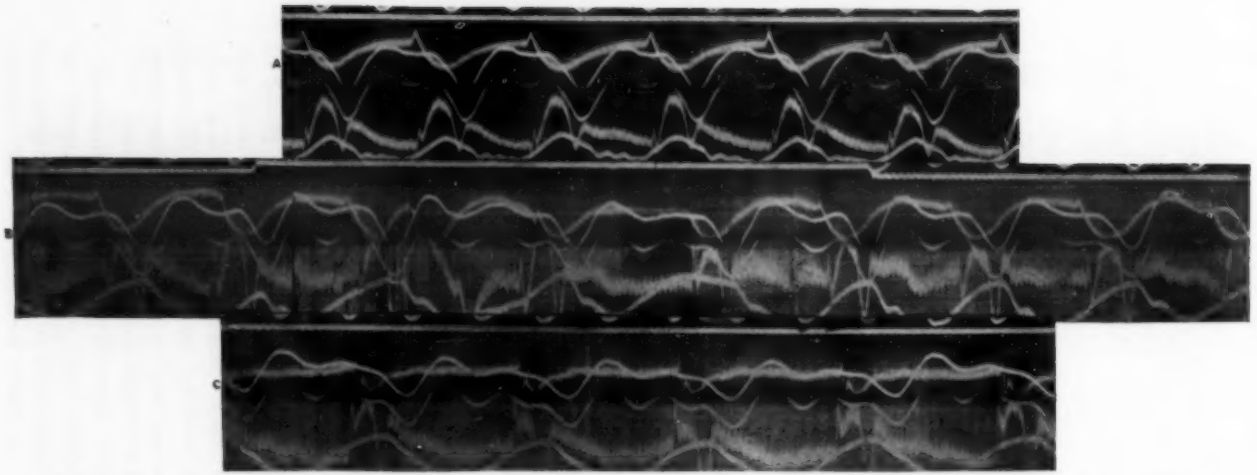

Fig. 4.—The records shown in this figure are to be interpreted as follows, reading from top to bottom: (1) Time record in one-fifth of a second intervals; (2) signal pen; (3) shadow of galvanometer fiber connected to upper and middle portion of sino-auricular node; (4) tambour lever, the downstroke of which indicates the onset of mechanical systole of the right auricle, there being immediately below this a duplicate shadow cast by this lever which should be ignored; (5) galvanometer fiber connected with two points on the auriculoventricular node; (6) tambour lever, indicating by its downstroke mechanical systole of the right ventricle.

The records are all from Experiment 51. *A* is the normal record and shows *Sa-Av* = 0.013 of a second, *As-Vs* = 0.10 of a second, cycle = 0.36 of a second. Between this and record *B* a ligature was tied above the sino-auricular node (interruption No. 3). As a result of this *Sa-Av* has increased, in the first cycle of this record, to 0.036 of a second. During record *B* a ligature was tied below the node (interruption No. 1), as signaled. This caused changes in the rhythm as follows: One auriculoventricular cycle with *Av-Sa* = 0.035 of a second, *As-Vs* = 0.04 of a second (cycle 2 of record); one normal cycle; one auriculoventricular cycle with *Av-Sa* = 0.032 of a second, *As-Vs* = 0.048 of a second, cycle = 0.43 of a second, one cycle with *Sa* and *Av* simultaneous, *As-Vs* = 0.08 of a second; then a succession of normal cycles with *Sa-Av* = 0.033, *As-Vs* = 0.093. Tying this ligature thus produced several auriculoventricular cycles, with permanent lengthening of the *Sa-Av* conduction period in the subsequent sino-auricular cycles.

C shows the condition of permanent auriculoventricular rhythm which developed, without further procedure, five minutes later. *Av-Sa* = 0.02 of a second, *As-Vs* = 0.032 of a second, cycle = 0.50 of a second.

was used and the onset in negativity in these different regions compared with the onset of mechanical systole of the right auricle. In the remaining thirty experiments two galvanometers were employed and the second method was used for the determination of the intervals of negativity. One galvanometer was connected with a pair of electrodes placed a few millimeters apart on one region to be compared; the other region had two similar electrodes connected with the second galvanometer. The two electrodes on the sino-auricular node were always connected with the galvanometer in such a way that the upstroke of the galvanometer curve indicated primary negativity in the uppermost of these two electrodes, thus giving additional information in those cases in which the node preceded other regions, whether the pacemaker was in its normal position in the upper part or lower down in the tissues of the node.[8]

SEQUENCE OF NEGATIVITY IN REGIONS NEAR THE SINO-AURICULAR NODE

The first ten experiments, summarized in Tables 1 and 2, show that points on the venous or intercaval side of the sino-auricular node usually manifest initial negativity before equidistant points on the auricular side, and that therefore the excitation should be regarded as spreading as a rule more rapidly in this direction than to the auricle. Experiments of a somewhat similar nature have been reported previously by us[4] and the same conclusion drawn. The present experiments, however, we believe lead clearly to a further conclusion, namely, that there is no restricted region surrounding the sino-auricular node which invariably receives the excitation before other regions. Considering the distance of any particular region from the node in its relation to the distance of other regions, we see no restricted region which can be regarded as the exclusive path of conduction.

Macroscopic examination of the dog's heart shows two large well-developed masses of musculature passing, respectively, from the upper and lower end of the sulcus terminalis. The former bundle has been described by Curran[9] in the calf's and sheep's heart as arising from the auriculoventricular node, passing upward along the interauricular septum, and consisting of bundles of musculature which can be traced almost to the mouth of the superior vena cava. That this bundle, however, has no especial significance in the conduction of the excitation from the sino-auricular to the auriculoventricular node is indicated by the fact that the electrodes placed on this structure (electrode 4 in the first four and electrode 8 in the last six experiments) did not

8. Meek and Eyster: Am. Jour. Physiol., 1914, xxxiv, 368.
9. Curran: Anat. Anz., 1909, xxxv, 89.

show negativity before electrodes on other regions equidistant from the node. The same can be said of the somewhat similar bundle, which apparently passes from the lower end of the sulcus terminalis downward toward the coronary sinus (electrode 9 in the first four, electrode 10 in the last six experiments). Furthermore, in two experiments (Experiments 9 and 10) these bundles were ligated during the course of the experiment without influencing the sequence as given in the tables.

SEQUENCE OF NEGATIVITY AND RATE OF CONDUCTION BETWEEN THE SINO-AURICULAR NODE, RIGHT AURICLE AND AURICULOVENTRICULAR NODE

The normal sequence of negativity between the sino-auricular node, right auricle and auriculoventricular node, as given in the normals of Table 4, further emphasize a fact for which we have already submitted evidence,[4] namely, that conduction from the sino-auricular node to the auriculoventricular node and ventricular conductive system does not normally occur, as has always been held, by way of the body of the right auricle, since the auriculoventricular node frequently receives the excitation before the body of the right auricle (atrium). In the normals of Table 4 the auriculoventricular node preceded in negativity the body of the right auricle in nine of twelve experiments. Measurements of the time intervals of the onset of negativity in the sino-auricular node, the right auricle and auriculoventricular node, as given in the normals of Table 5, while indicating in these experiments a more frequent occurrence of negativity in the right auricle before the auriculoventricular node, point to the same conclusion, because of the frequency of the reverse relation and the occurrence of practically simultaneous negativity in these two regions in other experiments. In twenty-four experiments in this series, the right auricle received the excitation before the auriculoventricular node in fifteen, with an average difference of 0.0091 of a second. The right auricle followed the auriculoventricular node in six experiments with an average of 0.0078 of a second. In three experiments the onset of negativity in the two regions was simultaneous, so far as could be determined from the records. That in any normal case negativity in the auriculoventricular node should precede that in the auricle would seem to preclude conduction to the node by way of the auricle as a normal process. As will be seen later in this paper, the results from the partial isolation of the sino-auricular node indicate most clearly that conduction from the sino-auricular node to the right auricle and the auriculoventricular node occurs by two separate and distinct paths under normal conditions. It may also be concluded that since the right auricle may, and frequently does, receive the excitation before the auriculoventricular,

the right auricle does not normally receive its excitation from the auriculoventricular node.

The normal time of conduction from the sino-auricular node to the auriculoventricular node (*Sa-Av*), as measured by the method of using two galvanometers simultaneously, averaged, in twenty-eight experiments, 0.023 of a second, with variations from 0.007 to 0.048 of a second. Conduction from the sino-auricular node to the beginning of the ventricular conductive system is thus quite rapid, and by far the greater part of the delay in passage to the ventricle must occur within the auriculoventricular node or bundle. The average time of conduction in the intact heart between the sino-auricular node and body of the right auricle or atrium (*Sa-Ra*) was 0.020 of a second in nineteen experiments, as determined by the same method, with variations between 0.012 and 0.04 of a second. With an average *As-Vs* interval of 0.12 of a second, it is evident that the excitation reaches the auriculoventricular node approximately 0.12 of a second before the ventricles enter into contraction. In a series of fourteen experiments previously reported by us[4] we found a somewhat higher average for the sino-auricular interval, using the first method of measurement described above, namely, 0.027 of second. We regard the method used in the present experiments more accurate and the result to represent more closely the correct value for this interval.

THE EFFECTS OF INTERRUPTION OF THE PATHS OF CONDUCTION

The influences exerted by partial or complete isolation of the sino-auricular node on *Sa-Av* and *Sa-Ra* conduction, and on the seat of the pacemaker, consequent on the procedures carried out in Experiments 11 to 66, are summarized in Table 6; Experiments 37 and 51, which were in auriculoventricular rhythm before any experimental procedures were carried out, are not included in this summary. The classification of the experiments in Table 6 is based on the situation of the single interruptions and the effects produced by isolation of the sino-auricular node on one or more sides.

The following points in reference to the effects produced would seem to be clear from the data presented:

Of the single interruptions, number 2, along the intercaval border of the sulcus, was the most effective in causing permanent auriculoventricular rhythm, which it did in 25 per cent. In 12.5 per cent. transitory auriculoventricular rhythm was established, making a total transitory and permanent removal of the pacemaker from the sino-auricular node of 37.5 per cent. Interruption number 3, across the sulcus above the sino-auricular node, produced transitory auriculoventricular rhythm in 40 per cent., but in no case was this rhythm permanently established, sino-auricular rhythm returning in all cases. Inter-

ruption number 1 caused transitory auriculoventricular rhythm in 10.5 per cent. and in 10.5 per cent. this rhythm was permanently established, a total of 21 per cent. Interruption number 4, along the auricular border of the sulcus, was clearly the least effective in causing a change in the location of the pacemaker, failing to produce in any of seventeen experiments either temporary or permanent removal.[10] Isolation of the node on the auricular side, on the other hand, was very effective in increasing the time of conduction between the sino-auricu-

TABLE 6.—SUMMARY OF RESULTS OF CUTS MADE AROUND THE SA NODE COMPILED FROM TABLES *

Cuts	Experiment	Sa Rhythm Persisted	Transitory Av Rhythm Developed	Percentage of Total Developing Transitory Av Rhythm	Permanent Av Rhythm Developed	Percentage of Total Developing Permanent Av Rhythm	Percentage of Those Not Developing Av Rhythm That Showed Increase of Sa-Av	Average Increase of Sa-Av, Sec.	Percentage of Those Not Developing Av Rhythm That Showed Increase of Sa-Ra	Average Increase of Sa-Ra
1	19	15	2	10.5	2	10.5	100	0.0115	29	0.0025
2	8	5	1	12.5	2	25	50	0.025	0	
3	10	6	4	40	0	0	100	0.0116	0	
4	17	17	0	0	0	0	14	.....	100	0.0115
1 and 2	16	6	4	25	6	38	100	0.0122	12.5	0.002
1 and 3	9	2	2	22	4	33	100	0.0150		
1 and 4	6	3	0	0	3	50				
2 and 3	4	2	0	0	2	50	50	0.015	0	0
2 and 4	5	1	0	0	4	80				
3 and 4	4	2	0	0	2	50				
1, 2 and 3	11	2	1	9	8	73	100	0.0135		
1, 2 and 4	5	2	0	0	3	60				
1, 3 and 4	4	2	0	0	1	25				
2, 3 and 4	3	1	0	0	2	66				
1, 2, 3 and 4	10	0	.....	.....	10	100				

* Experiment 26, in which Cut 4 was not completed, is not included in the summaries. Experiments 37 and 51, in which Av rhythm was present before any cuts were made, were not included in the summaries. The results in one case of Cut 2 and one case of Cuts 3 and 4 are doubtful and are not included in the summary.

lar node and the right auricle (*Sa-Ra*), which it did in 100 per cent. of all cases (eight) in which this was measured. The average increase was 0.0115 of a second. The other interruptions failed to cause any increase in *Sa-Ra* conduction time, except in number 1, which showed an apparent increase of 0.0025 of a second in 29 per cent. of the cases,

10. Experiment 37, in which such a change did occur, is excluded from the totals, since examination showed that the interruption involved a considerable portion of the sino-auricular node.

an amount probably too small to possess any significance and close to the limit of accurate measurement. Conduction from the sino-auricular to the auriculoventricular node (*Sa-Av*), in those cases in which the seat of impulse formation remained in the sino-auricular node, was much less frequently increased by isolation on the auricular side of the node than on the other sides. Interruption number 4 produced this effect only once in seven experiments (1 per cent.). Interruption of the intercaval connections caused an increase in this time in three of six experiments, interruption of the connections below the node in all of seventeen experiments, and interruption above the node in all of ten experiments. The general average of increase in *Sa-Av* conduction from interruptions 1, 2 and 3 was 0.0121 of a second. It therefore seems clear that interruptions above, along the intercaval border and below the sino-auricular node interfere more or less in almost all experiments with conduction from the sino-auricular to the auriculoventricular node. This interference may be sufficient to block the impulse completely and lead to auriculoventricular rhythm, or it may merely prolong the period of conduction. These do not interfere, to any important degree, with conduction from the sino-auricular node to the right auricle. This latter effect is the pronounced influence exerted, however, by interruption of the connections along the auricular side of the node. Such interruption, however, rarely influences conduction from the sino-auricular to the auriculoventricular node.

Isolation of the node on two sides was more effective in producing a change in the seat of the pacemaker than isolation on any one side. Interruptions 2 and 4 were apparently the most effective, permanent auriculoventricular rhythm being established in 80 per cent. of all cases. The other combinations were about equal in reference to number of transitory and permanent changes in the pacemaker. Interruptions 1 and 3 formed a total of 63 per cent. of permanent (38 per cent.) and transitory (25 per cent.) auriculoventricular rhythms and consistently increased *Sa-Av* conduction in those cases in which this rhythm was not permanently established. On interruption of the connections on three sides of the node, interruptions 1, 2 and 3 had the greatest effect, producing permanent (73 per cent.) or transitory (9 per cent.) auriculoventricular rhythms in 82 per cent. of all cases, and in all the remainder increasing *Sa-Av* conduction time. Interruptions 1, 2 and 4, and 2, 3 and 4 produced less effect in those experiments than when 2 and 4 were made alone, probably indicating that the incidence of 80 per. cent. of permanent auriculoventricular rhythm from 2 and 4 alone is high and would be reduced by a longer series of experiments. Interruption of the connections of the sino-auricular node on all four sides produced permanent auriculoventricular rhythm in all of ten experiments.

POSSIBILITY OF INFLUENCES EXERTED THROUGH ANEMIA OR THROUGH THE VAGUS MECHANISM

It was thought possible that one or both of two influences, associated with the isolation of the node, other than that of interruption of paths of conduction, might play a part in the results obtained, namely, (1) decrease in blood supply to the sino-auricular node, (2) mechanical or other stimulation of cardio-inhibitory fibers, in the neighborhood of the lesions. In reference to the first possibility, Keith and Flack,[11] Koch[12] and others have called attention to the abundant blood supply to the node. A prominent branch of the right coronary artery passes through the long axis of the node to unite above with a branch from above, forming what has been termed the circulus arteriosus sino-auricularis. Numerous branches are given off from this artery in its passage through the node. In several experiments we have tied the main vessel supplying the node without, however, the node losing its function as pacemaker and without producing any measurable change in conduction from the node to the auricle or to the auriculoventricular node. In this connection it is important to note that interruptions 1 and 3 were those which abolished the direct supply of blood to the node through the coronary arteries, after which the node was supplied with blood only through anastomoses on the venous and auricular side and by direct contact of the blood within the heart cavity. The fact that interruption 2, along the venous border of the node, was the most effective in permanently abolishing sino-auricular rhythm, while it probably interfered least of any with the blood supply, would further indicate that decrease in the blood flow to the nodes was not a very important factor in causing a loss of the pacemaking function by this structure. The main factor in the loss of this function and its assumption by some other region, as a result of partial isolation of the node, would therefore seem to be due more to interruption of paths of conduction from the node to the remainder of the heart and a consequent decrease or loss of its influence on the heart as the seat of dominant automaticity, rather than to a reduction in its automaticity below the point of dominance by anemia. In several experiments we have obtained clear proof that the sino-auricular node may continue to function and discharge impulses at a higher rate than the auriculoventricular node at a time when the latter is acting as pacemaker for the heart, the impulses from the former being prevented from reaching other parts of the heart because of interruption of the paths of conduction. This condition is complete sino-auricular and sinoventricular heart block. The discussion of these experiments in detail will be

11. Keith and Flack: Jour. Anat. and Physiol., 1907, xli, 172.
12. Koch: Med. Klin., 1912, viii, 108; ibid., 1913, ix, 1.

found in a subsequent paper. We have seen the sino-auricular node in the heart in situ, but completely separated from all physiologic connection with the remainder of the heart, continue in activity at approximately its normal rate for considerable periods of time. Under these circumstances the interruption of its circulation through the coronary arteries is complete and it receives its blood supply only by contact with the blood within the interior of the heart. Perhaps the same degree of anemia, if acting for a prolonged period of time, would ultimately depress the tissues to the point at which activity would be much reduced or would disappear. It will be noted in Tables 3 and 5 that not infrequently interruptions which did not cause a removal of the seat of the pacemaker from the sino-auricular node produced a slight slowing of the rate of discharge, as is evident from the somewhat longer cycle. This increase in length of cycle indicates a slight reduction in the automaticity of this region, caused perhaps by partial interruption of its blood supply. It would seem, therefore, that while reduction in the blood supply as a result of interrupting the connections of the node may have been in our experiments in some or all cases a contributing factor in the loss by this region of its function as pacemaker for the heart, it was not the most important factor in this change. The latter, we feel, must be referred to interruption of the paths of conduction to other regions and as a consequence the blocking of the impulses from the sino-auricular node until the automaticity of some other region assumed dominance.

The possibility that the effects produced by isolation of the node by clamping or cutting might be ascribed to an effect produced through the vagus, we have eliminated by the administration of atropin in amounts sufficient to completely paralyze the vagus mechanism throughout the course of the experiment. This procedure has been carried out in a sufficient number of experiments to establish the fact that it is without effects on the results produced.

SINO-AURICULAR AND SINOVENTRICULAR CONDUCTION PATHS

We believe that our experiments point clearly to the conclusion that there is no single, well-defined and localized path which serves to the exclusion of others for the conduction of the excitation from the sino-auricular to the auriculoventricular node. At least it may be said that if there is such a path, other paths are present which are capable of conducting the excitation with almost equal facility. As the possible connections between these two nodes are gradually interrupted, there are two results which come out clearly in most of the experiments, first, a lengthening of the time of conduction, and second, its abolition. The latter is associated with the removal of the impulse initiation to the auriculoventricular node. It seems to us that these

results may be interpreted in one of two ways, either that a diffuse path of conduction between the two nodes normally exists, including perhaps all of the tissue surrounding the sino-auricular node except along its auricular border, and that interruption of any part of this path delays or finally abolishes conduction merely by restricting the path to an amount of tissue too small to conduct, or it may be supposed that a part of this represents a more or less well-localized path in which conduction occurs under normal conditions with greatest facility and most rapidly. Removal of this would result in conduction, at a slower rate, over other paths. It may be said, finally, that if there is such a localized path of least resistance its exact position must vary in different hearts. Certain of our experiments indicated the possibility of such a path existing across the intercaval tissues, since it is this region which usually receives the excitation somewhat earlier than the tissues above or below the sulcus terminalis, and further, that interruption 2, which severed this connection, was on the whole the most effective one in abolishing sino-auricular rhythm. It should be noted, however, that the separation of tissue involved in this cut was greater than in either interruption 1 or 3, and that, furthermore, since sino-auricular rhythm may be abolished or *Sa-Av* conduction time definitely increased from either interruption 1 or 3, the assumption of this intercaval path as the path of least resistance does not hold in many cases. Interruptions 1 and 3 either caused a change in the seat of the pacemaker or a lengthening of the *Sa-Av* conduction time in all cases in which this was determined in our experiments, and there would seem, therefore, to be as much and perhaps more reason to ascribe to one or the other of these connections the path of least resistance.

The results from interruption of the connections on different sides of the sino-auricular node, however, serve to distinguish clearly two definite and distinct paths, by one of which the excitation is conducted from this node to the right auricle, by the other from the node to the auriculoventricular node and ventricular conductive system. Interruption 4, which severed the direct continuity of the sino-auricular node and the tissues of the right auricle except for possible small connections at the upper and lower extremities of the node, increased the conduction time between the sino-auricular node and the right auricle in all of seventeen experiments. In none of these did it cause a removal of the seat of impulse initiation from the sino-auricular node, and in only 14 per cent. was there any increase in conduction between this node and the auriculoventricular node. On the other hand, interruptions, 1, 2 and 3, which severed possible paths of conduction below, on the intercaval side and above the node, in the great majority of instances caused either the development of auriculoventricular rhythm or lengthened *Sa-Av* conduction time. The influence of this interruption on *Sa-Ra* conduction time, in those cases in which it apparently

occurred, was too small to be of any significance. These results confirm by another method a conclusion at which we have previously arrived,[4] namely, that normally conduction from the sino-auricular node to the right auricle, on the one hand, and to the auriculoventricular node, on the other hand, occurs by separate paths. The excitation, arising normally in the sino-auricular node, spreads directly to the right auricle, probably in a diffuse manner, from the auricular side of the node. It also spreads to the auriculoventricular node by paths, probably also diffuse in nature, connecting with the upper, intercaval border and the lower end of the sino-auricular node. We cannot, therefore, in accuracy speak of auriculoventricular conduction in the normal dog's heart. There is an auriculoventricular interval, which is determined by the conduction in three paths, namely, (1) between the sino-auricular node and the right auricle, (2) between this node and the auriculoventricular node, and (3) between the auriculoventricular node and the ventricles.

While it is clear in the normal dog's heart conduction from the sino-auricular node to the auriculoventricular node does not occur by way of the auricle, conduction in this manner may occur in certain cases when the normal paths of *Sa-Av* conduction are interrupted. Sino-auricular rhythm may continue (27 per cent. in eleven experiments), in which the sino-auricular node is cut off from all connections except the auricle. Conduction to the auriculoventricular node in those cases can occur only by way of the right auricle. Reference to the tables will show that these instances showed abnormally long *Sa-Av* conduction periods.[13] It is possible that connections between the right auricle and auriculoventricular node exist in all cases, but conduction over this path is more difficult than the normal sinoventricular path. In a majority of cases possible conduction to the auriculoventricular node by way of the right auricle would seem to be so difficult that auriculoventricular rhythm develops when the normal functional path between the sino-auricular and auriculoventricular nodes is interrupted.

RELATIVE AUTOMATICITY OF THE SINO-AURICULAR NODE, THE AURICULAR PORTION OF THE AURICULOVENTRICULAR NODE (CORONARY SINUS), AND THE VENTRICULAR PORTION OF THE AURICULOVENTRICULAR NODE

Those experiments in which auriculoventricular rhythm developed as a result of partial or complete isolation of the sino-auricular node make it possible to determine the automaticity or rate of impulse

13. Note also, as shown in Table 4, that under these circumstances the auriculoventricular node always followed the right auricle in negativity, usually a reversal of the normal relation in these experiments.

formation of this region, as compared with the normal pacemaker, the sino-auricular node. We[8] have previously shown that the upper and lower end of the sino-auricular node differ in automaticity, and Zahn[14] has shown similar differences within the auriculoventricular node. When auriculoventricular rhythm develops as a result of loss of the influence of the sino-auricular node, it is reasonable to assume that the seat of impulse formation is in the most automatic portion of the auriculoventricular node. It is this part, therefore, and its relation to the automaticity of the sino-auricular node which possesses the greatest interest. In a few of our experiments, after loss of the pacemaking function by the sino-auricular node, the seat of impulse initiation was found to be in the region surrounding the mouth of the coronary sinus, a part of the system of nodal tissues, which is connected with and forms a part of the auriculoventricular node. Aschoff,[6] who first demonstrated this connection, designated it as the auricular portion of the auriculoventricular node, while the main mass of this node, lying within the interauricular septum, was termed the ventricular portion. It is this latter part from which the auriculoventricular bundle and ventricular conductive system arises.

Coronary sinus rhythm is usually, but not always, associated with shortening of the *As-Vs* interval and increase in length of the cycle over that present in sino-auricular rhythm. The *As-Vs* interval has not been less than 0.04 of a second in any instance in our experience. Probably the only absolutely definite criterion for coronary sinus rhythm is the occurrence of initial negativity in the coronary sinus region. In our experience, however, the occurrence of practically simultaneous negativity in the sino-auricular node and the ventricular portion of the auriculoventricular node has been always associated with the seat of impulse initiation in the coronary sinus region.

The condition in which the seat of impulse initiation is in the ventricular portion of the auriculoventricular node, auriculoventricular rhythm, is likewise probably only definitely determined by the localization of initial negativity in this region.[15] Shortening of the *As-Vs* interval to less than 0.04 of a second or the presence of a *Vs-As* interval in a continuous rhythm in which the auriculoventricular node was intact, has always been associated with the pacemaker in this node

14. Zahn: Arch. f. d. ges. Physiol., 1913, cli, 247.

15. The use of local heating as a method for determining the location of impulse initiation, which has been somewhat extensively employed in recent work, particularly by Ganter and Zahn and by Zahn, is open to the objection that the response of a certain region may be the result of increase of its automaticity by the heat until it becomes the pacemaker, and does not necessarily mean that it was the seat of impulse initiation before the heat was applied. Local cooling may likewise drive the pacemaker to some other region. The electrical method seems certainly to offer the least objection.

in our experience. In other cases of auriculoventricular rhythm the shortening of the *As-Vs* interval has been slight, although uniformly present. Reference to Table 5 will show one case in which the *As-Vs* interval was 0.13 of a second, two cases in which it was 0.09 of a second, one in which it was 0.08 of a second and one in which it was 0.07 of a second. Decision as to the presence or absence of auriculoventricular rhythm, on the basis of the *As-Vs* interval, would seem to be valueless unless this interval shortens to 0.03 of a second or below, or becomes reversed (*Vs-As*). A moderate shortening of the *As-Vs* interval may be associated with (1) removal of the pacemaker to the lower end of the sino-auricular node,[8] (2) development of coronary sinus rhythm, (3) development of auriculoventricular rhythm, (4) probably in certain cases with no change in the seat of impulse initiation, but as a result of changes in conduction. To decide definitely which one of these is the associated condition, one must determine the seat of impulse initiation by the electrical method or by local heating or cooling.

In thirty-four experiments[16] the heart in auriculoventricular rhythm, in which the seat of impulse initiation was in the ventricular portion of the auriculoventricular node, showed an increase in length of the cycle in percentage of the cycle of normal sino-auricular rhythm of an average of 33 per cent. The most automatic portion of the auriculoventricular node in the dog's heart may therefore be regarded as having an average automaticity equal to 67 per cent. of the automaticity of the sino-auricular node. In other words, if the average dog's sino-auricular node is capable of initiating impulses at the rate of 100 per minute, the auriculoventricular node has the power to initiate impulses, when freed from the domination of the sino-auricular node, of 67 per minute. Great variations are encountered, however, in different animals. In the thirty-four experiments the decrease in rate associated with the development of auriculoventricular rhythm varies from 5 per cent. to 82 per cent. An average of eighteen experiments, in which during the auriculoventricular rhythm there was a *Vs-As* interval or an *As-Vs* interval of less than 0.04 of a second, showed an average decrease over the original sino-auricular rate of 37 per cent. An average of fifteen, in which the *As-Vs* interval was 0.04 of a second or longer, showed a decrease of 29 per cent. The decrease in rate would seem, therefore, to be somewhat greater when there was a marked change in the *As-Vs* interval. There are, however, wide variations in the individual cases from the averages.

16. One experiment was omitted from the averages (Experiment 58) because it differed so widely from the remainder and showed normally an excessively long *As-Vs* interval.

Coronary sinus rhythm showed an average reduction of 29 per cent. in rate of impulse formation as compared with the normal sino-auricular rhythm in seven experiments, indicating an average automaticity of this region equal to 71 per cent. of the normal sino-auricular rhythm. The extreme variations in the different experiments were 13 per cent. and 77 per cent. In one experiment (Experiment 19), the great difference between the automaticity of the sino-auricular node and the region of next lower automaticity (77 per cent.) was further indicated by the necessity of completely isolating the sino-auricular node on all four sides before the seat of impulse initiation changed (to the coronary sinus region). If this experiment is left out of the average, the reduction of the automaticity in coronary sinus rhythm amounted to only 20.5 per cent. of the previous automaticity, with variations between 13 per cent. and 33 per cent.

It would seem clear from the data presented above that the coronary sinus region or the auricular portion of the auriculoventricular node may show a somewhat higher automaticity than the ventricular portion of the same node in certain animals under certain conditions. Further, the general average of coronary sinus automaticity, when developed, is somewhat higher than that of the ventricular portion of the auriculoventricular node. The usual result of ablation of the sino-auricular node is, however, the assumption of impulse by the latter region. This, as we have seen, occurred in thirty-four of forty-one experiments in this series (83 per cent.). It is difficult to understand why coronary sinus rhythm does not develop more frequently on the basis of the average comparative automaticity of this region. On the basis of the well-known fact that automaticity may be increased by stimulation, it is possible that the somewhat exposed position of the coronary sinus region as compared with that of the ventricular portion of the auriculoventricular node leads under certain experimental conditions to the development of an abnormal degree of automaticity in the former region, and in these exceed the normal automaticity of the latter. Brandenburg and Hoffmann[17] were the first to note the tendency of a rhythm other than the usual auriculoventricular rhythm to develop when rather rough mechanical procedures, such as clamping, were used to destroy the sino-auricular node. The authors thought the pacemaker, under these circumstances, was in a diffuse area in the right auricle, but Zahn[14] later showed that it was a coronary sinus rhythm with the pacemaker in the auricular portion of the auriculoventricular node. We[1] have reported similar experiences in a preceding paper of this series.

17. Brandenburg and Hoffmann: Med. Klin., 1912, viii, 16.

CONCLUSIONS

1. In the dog's heart the cardiac impulse, arising within the upper part of the sino-auricular node, is conducted to the right auricle and to the auriculoventricular node by two separate paths. The former is a diffuse path represented by the contact of the right auricle with the node. The latter path is either also diffuse in nature, involving connections above, below and on the intercaval borders of the node, or there are numerous possible paths offering varying degrees of resistance to the passage of the impulse.

2. The normal period between the occurrence of negativity in the sino-auricular node and in the right atrium averages 0.02 of a second in the dog's heart in situ. The average period of conduction between the sino-auricular node and the ventricular portion of the auriculoventricular node is 0.023 of a second. These conduction periods may be increased from two to two and a half times by partial interruption of the paths concerned.

3. The effects of partial elimination of the connections between the sino-auricular node and the auriculoventricular node are the occurrence of an increased period of conduction between the sino-auricular and auriculoventricular nodes; the cessation of conduction over the normal path with conduction by way of the right atrium; and the cessation of the conduction over the normal path and the occurrence of auriculoventricular rhythm or coronary sinus rhythm.

4. The effects of complete interruption of functional connections between the sino-auricular node and other parts of the heart, or reduction of these connections below a certain value, results in removal of the seat of impulse initiation. In a total of forty-one experiments, in thirty-four the pacemaker was located in the ventricular portion of the auriculoventricular node, in seven in the auricular portion of this node (coronary sinus region).

5. In the dog's heart under the conditions of these experiments, the ventricular portion of the auriculoventricular node showed the capacity to develop automaticity equal to an average of 67 per cent. of the normal automaticity of the sino-auricular node. The auricular portion of the auriculoventricular node showed a similar average of 71 per cent. of the degree of sino-auricular automaticity, although this region developed automaticity much less frequently than the ventricular portion of the auriculoventricular node.

A METABOLISM STUDY OF GOITER

WITH THE EFFECT OF THYROID AND THYMUS TREATMENT *

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Many studies on the feeding of thyroid and thymus have been made on various animals and man, in normal and in pathologic conditions. The results obtained have in many cases been contradictory, although the majority of observers agree that loss of weight and increase of protein metabolism occur in the feeding of thyroid gland to normal animals and man, and that the effect on metabolic processes is more marked in hypothyroidism and in hyperthyroidism. The results with thymus feeding have so far not been encouraging.

Scholz[1] conducted rather complete experiments with a woman suffering with exophthalmic goiter and with a normal person on the same treatment for comparison. Each subject was studied for two periods of from three to five days each, one without thyroid treatment and the other on dried thyroid gland substance. His goiter patient, without treatment, stored 7.437 gm. and on thyroid substance 7.09 gm. nitrogen per day. For the normal control with thyroid treatment the daily nitrogen retention fell from 3.76 to 2.64 gm. That the data from this patient were typical has not yet been demonstrated, but similar though less marked results have been obtained on animals by Roos and others. Roos,[2] using a dog weighing 11.943 kg., to which 25 gm. of fresh thyroid were given for six days, records an increase of urinary nitrogen from 4.32 to 6.27 gm. and a diminution of 1.82 kg. in weight. A further dose of 30 gm. fresh gland caused a decrease to 4.09 gm. urinary nitrogen and a lowering of body weight to 9.956 kg. Roos showed that the administration of thyroid substance to a thyroidectomized dog increased the nitrogen and sodium chlorid elimination to a greater degree than when thyroid was given to the normal dog. He concluded that the thyroid has a decided influence on phosphorus and nitrogen metabolism, the nature of which was as yet obscure.

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1. Scholz: Zentralbl. f. inn. Med., 1895, xvi, 1041, 1069.
2. Roos: Ztschr. f. physiol. Chem., 1895, xxi, 19.

A patient of Matthes,[3] who was given her own dried excised gland, showed increased nitrogen excretion. David's[4] patient, on thyro-iodin, excreted 90 per cent. more nitrogen. Scholz[1] and Hirschloff[5] in similar cases of exophthalmic goiter report retention of nitrogen and gain in weight.

Magnus-Levy[6] established the fact that in exophthalmic goiter the energy requirements increased from 50 to 70 per cent. above the normal and he showed in cretinism and myxedema[7] that the heat production was as much as 45 to 50 per cent. below normal; that thus the respiratory quotient in the above diseases is low, but in exophthalmic goiter[8] high. Dubois[9] gave an instance of a cretin whose total energy requirement was increased by thyroid treatment from 18 to 25 per cent. above the normal. Magnus-Levy[8] and Anderson and Bergmann[10] also found thyroid gland produced marked effects of this nature on normal men.

Schöndorff,[11] using a dog as subject, obtained a loss of nitrogen of 0.66 gm. in a twelve days' foreperiod, and of 0.12 and 1.13 gm., with a loss in weight in two periods of forty-six days under the influence of varying doses of dry and fresh gland respectively. Schöndorff considered that the protein metabolism at first was not affected; that the body fat was used up, and that increased nitrogen output was due to an increased excretion of nitrogenous extractives, already formed and retained in the body. He considered that protein metabolism was later upset.

Georgiewsky, Richter, Gluzinski and Lemberger, Voit, and Ostwald[12] also obtained with thyroid feeding loss of weight in dogs. Schäfer[13] found that the addition of small amounts of thyroid tissue to the diets of white rats greatly increased the food consumption, especially in quite young individuals, and accelerated growth and nitrogen retention. Farrant[14] in a recent paper reports increased appetite and loss of weight in cats and in rabbits after thyroid feeding. Hewitt[15]

3. Matthes: Verhandl. d. Cong. f. inn. Med., 1897, 232.
4. David: Ztschr. f. Heilk., 1897, xvii, 439.
5. Hirschloff: Ztschr. f. klin. Med., 1899, xxxvi, 200.
6. Magnus-Levy: Berl. klin. Wchnschr., 1895, xxx, 650.
7. Magnus-Levy: Ztschr. f. klin. Med., 1904, lii, 201.
8. Magnus-Levy: Ztschr. f. klin. Med., 1897, xxxiii, 269; Ibid., 1906, lx, 177.
9. Dubois: Jour. Am. Med. Assn., 1914, lxiii, 827; THE ARCHIVES INT. MED., 1916.
10. Anderson and Bergmann: Skand. Arch. f. Physiol., 1898, viii, 326.
11. Schöndorff: Arch. f. d. ges. Physiol., 1897, lxvii, 385.
12. Georgiewsky: Ztschr. f. klin. Med., 1897, xxxiii, 153. Richter: Centralbl. f. inn. Med., 1896, xxii, 65. Gluzinski and Lemberger: Centralbl. f. inn. Med., 1897, xviii, 89. Voit: Ztschr. f. Biol., 1897, xxxv, 116. Ostwald: Ztschr. f. physiol. Chem., 1899, xxiv, 39.
13. Schäfer: Quart. Jour. Exper. Physiol., 1912, v, 203.
14. Farrant: Brit. Med. Jour., 1913, ii, 1363.
15. Hewitt: Quart. Jour. Physiol., 1914, viii, 113.

found that 0.5 gm. doses of thyroid administered to rats gave a greater nitrogen retention than larger doses.

Scholz, Richter, and Gluzinski and Lemberger obtained a diminished positive nitrogen balance after thyroid administration. Cramer and Krause[16] found that the administration of thyroid gland affected carbohydrate metabolism. A further proof of this action on carbohydrate and also on fat metabolism is afforded by the observations of Thiele and Nehring and Stüve[17] that in the case of a normal man to whom thyroid was given the gaseous exchange was greatly increased.

On the other hand, the administration of the gland has in some cases in man (Magnus-Levy) and in dogs (Underhill and Saiki and Rahel Hirsch[18]) been found to cause no alteration in metabolism. Similar results in the case of a normal man were obtained by Magnus-Levy[19] who found no distinct increase of oxygen intake or carbon dioxid output while administration of thyroid to a patient with myxedema caused an increase in oxygen intake of 80 per cent. Underhill and Saiki found that thyroid fed to normal dogs effected a slight increase in urinary nitrogen. Small doses appear to have as pronounced an effect as larger ones. In the case of two patients, Scholz and Hirschloff observed with marked daily gain in weight not the slightest disturbance in nitrogen balance.

Unlike thyroid, thymus fed or injected into animals has appeared to have no effect on nitrogen metabolism. Extirpation experiments, however, indicate some connection between the thymus and growth of the skeleton, that is, calcium metabolism.

Carbone[20] appears to have found on thymectomized dogs and rabbits a slight increase in nitrogen in both urine and feces. Mikulicz, Reinbach, and Cunningham[21] report an effect on goiter by thymus, similar to that of thyroid. Magnus-Levy reports two cases in which feeding thymus in exophthalmic goiter for longer or shorter periods was found tó have no effect on oxygen consumption. Basch[22] on thymectomized animals in comparison with controls of the same litter

16. Cramer and Krause: Proc. Roy. Med. and Chir. Soc., London, 1913, lxxxvi, 550.

17. Thiele and Nehring: Ztschr. f. klin. Med., 1896, xxx, 41. Stüve: Festschr. der Stadtischen Krankenhauses im Frankfort-am-Main, September, 1896.

18. Underhill and Saiki: Jour. Biol. Chem., 1908, v, 225. Hirsch: Oppenheimer's Handbuch der Biochemie, Jena, 1910, iii, 271.

19. In Von Noorden: Metabolism and Practical Medicine, American edition, Chicago, 1907, iii.

20. Carbone: Gior. d. r. Accad. di med. di Torino., 1897, ix, 7.

21. Mikulicz: Berl. klin. Wchnschr., 1895, xxxii, 342. Reinbach: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1898, iii, 309. Cunningham: Jour. Exper. Med., 1896, iii, 227.

22. Basch: Ztschr. f. exper. Path. u. Therap., 1905, ii, 95.

obtained twice as great a calcium excretion. Roos[23] on a dog found that child's thyroid, with an iodin content of 0.025 per cent., given in doses of 5 gm. of dried substance caused no effect, while gland containing 0.18 per cent. in like amount produced increased nitrogen excretion.

Age affects the results obtained in an artificially produced condition of hyperthyroidism. Vermehren[24] states that patients of over 50 years of age show a greater increase of protein metabolism than children, while Georgiewsky[12] found that in dogs the reverse was the case, young animals reacting more readily than adults.

Perhan[25] studying the influence of thyroid principle on calcium metabolism in rabbits, showed that the ingestion of thyroid caused a loss of calcium from the tissues, which ran parallel to the amount of thyroid ingested. Falta, Bolaffio, and Tedesco[26] after parathyroidectomy found that thyro-iodin brought about increased excretion of calcium in the feces.

Schäfer,[13] feeding thyroid to white rats, observed an increased calcium and magnesium excretion. His average variations are considerable and so render the results somewhat doubtful. In a case of myasthenia gravis, which may be an intoxication, Diller and Rosenbloom[27] have shown that a marked loss of calcium from the tissues obtains by way of the urine. In a period of eight days they found that 5.7 gm. of calcium oxid, out of a total excretion of 6.3 gm., was eliminated by this channel. Pemberton[28] also obtained in myasthenia gravis a similar loss of calcium from the tissues. Scholz found an increased excretion of alkaline earth elements in three cretins. He made complete mineral balances and concluded as a result of his extensive experiments that the metabolism in cretins is sluggish. Basch[29] found that injections of soluble calcium salts brought back the irritability to normal in the case of thymectomized dogs with changed psychical nature. Attempts[30] have been made to explain the influence on calcification by ascribing to the thymus a detoxicating action in building up acids circulating in the blood into nucleoprotein of the thymus. This suggestion has not been supported by sufficient experi-

23. Roos: Ztschr. f. physiol. Chem., 1899, xxviii, 40.
24. Vermehren: Deutsch. med. Wchnschr., 1893, xix, 255, 1037.
25. Perhan: Compt. rend Soc. de biol., 1913, lxxii, 620.
26. Falta, Bertelli, Bolaffio, Tedesco, and Rudinger: Verhandl. d. Cong. f. inn. Med., 1909, xxvi, 138.
27. Diller and Rosenbloom: Am. Jour. Med. Sc., 1914, cxlviii, 65.
28. Pemberton: Am. Jour. Med. Sc., 1910, cxxxix, 816.
29. Basch: Jahrb. f. Kinderh., 1906, lxiv, 285; Wien. klin. Wchnschr., 1903, xxxi, 893; Deutsch. med. Wchnschr., 1913, xxxix, 1456.
30. Dmitricwski: Jahresb. ü. d. Fortschr. d. Thierchem., 1900, xxx, 778.

mental evidence. Towles[31] found no disturbance in the metabolism of calcium in exophthalmic goiter.

The older investigators on phosphorus metabolism during thyroid feeding determined phosphorus in the urine alone; they failed to consider fecal elimination. In thyroid feeding to normal men or animals or after thyroidectomy in both, the phosphorus may be excreted in increased amount either in the urine or feces. The amount depends on the size of the dose given. Phosphorus excretion may follow the nitrogen elimination or there may be a retention of phosphorus. Scholz found in a metabolism study of exophthalmic goiter (in a woman) that without thyroid treatment there was a loss of 2.09 gm. per day. In the case of a normal man ingesting thyroid the phosphorus pentoxid loss increased from 2.996 to 3.831 gm. per day.

There was no great increase of phosphorus in the urine with either subject, but in the feces the phosphorus elimination of the patient with goiter was increased to ten times the amount and that of the normal subject about 25 per cent. Since there was no such increase of nitrogen as of phosphorus outgo, Scholz believed that the latter was due to phosphate rather than nuclein metabolism. Richter[12] and Schiff[32] confirmed these results. Anderson and Bergmann and Burger[33] found that with thyroid ingestion in the nonmyxedematous total phosphorus excretion was marked, amounting in the urine alone to 1 gm. above the amount ingested. Senator[34] confirmed these results. Burger's researches showed that the amount of ingested thyroid quantitatively governed the nitrogen and phosphorus pentoxid excretion. Roos in experiments on healthy dogs found that the administration of thyroid gland substance in large doses caused an increased phosphorus as well as sodium chlorid and nitrogen excretion. The increased phosphorus excretion continued longer than that of sodium chlorid. In a thyroidectomized dog, feeding of thyroid did not increase the phosphorus excretion to a greater degree than in the normal dog, but it remained considerably below normal. Roos noted evidence sustaining the idea that phosphorus as well as nitrogen assimilation requires the assistance of the secretory product of the thyroid.

Ord and White,[35] studying thyroid treatment in myxedema, noted a slight total increase in phosphorus metabolism. Richter found that the phosphorus excretion exceeded that of nitrogen. Schafer showed on white rats that the extent of increase of phosphorus excretion depended on the quantity of thyroid ingested, which had to be increased

31. Towles: Am. Jour. Med. Sc., 1910, cxl, 100.
32. Schiff: Ztschr. f. klin. Med., 1897, xxxiii (supplementary number), 284.
33. Burger: Inaug. Diss., Halle, 1895.
34. Senator: Berl. klin. Wchnschr., 1897, xxxiv, 109.
35. Ord. and White: Brit. Med. Jour., 1893, ii, 216.

beyond a certain point before any results were obtained. However, Scholz in his studies on the three cretins above referred to concluded that the phosphorus retention is considerable on small intake, and does not increase in proportion to intake.

The results with thyroid feeding following thyroparathyroidectomy or thyroidectomy alone, may vary even more. There may be a subnormal elimination of phosphorus, a retention, or a return to normal metabolism or an increased phosphorus elimination. Underhill and Saiki[36] observed a low output of phosphorus and a high output of purin nitrogen after the continued administration of large doses of thyroid tissue to dogs. Saccone[36] observed that the urinary phosphorus rose to three times the previous amount after removal from a dog of both the thyroids and parathyroids. The feeding of thyroiodin in addition to the normal diet reduced the excretion of phosphorus to the original low level. Roos showed that the administration of thyroid substance to a thyroidectomized dog did not increase the phosphorus elimination. After performing thyroidectomy in dogs, Ushenko[37] stated that the relation of the percentage of phosphorus to nitrogen in the urine first increased and later diminished. Similar results were obtained for ammonia. He concluded that the metabolism of phosphorus and nitrogen was acutely disturbed and that the synthetic processes were the ones mainly affected.

Magnus-Levy,[10] discussing the metabolism of sulphur in exophthalmic goiter, says that nothing is known about its excretion either as to amount or its balance. The catabolism of sulphur, however, as shown by Daddi and Marchetti[38] varies as little from the normal as do the constituents of the nitrogen partition in protein metabolism. The excretion of sulphur after thyroid feeding of the nonmyxedematous frequently rises (Pfeiffer and Scholz[39] and Georgiewsky[19]), according to Burger,[19] as high as 60 per cent., or much higher than the rise in nitrogen, though this result is not constant. Pfeiffer and Scholz found that the sulphur excretion rose to about the same extent as that of nitrogen, after thyroid feeding.

Sulphur excretion may parallel that of nitrogen or rise above it. Hirschstein[40] recently reported conclusions only of metabolism studies during long-continued thyroid medication, in which in a certain type of hypothyroidism, designated the asthenic, readily leading to great emaciation, there was a high excretion of sulphur, nitrogen, and phos-

36. Saccone: Ann. di med. navale, 1907, 13, i, 573.
37. Ushenko: Russk. Vrach., 1913, 1751; Chem. Abstr., 1913, vii, 3150.
38. Daddi and Marchetti: La Clinica Moderna, No. 1; Biochem. Centralbl., 1904, ii, 752.
39. Pfeiffer and Scholz: Oppenheimer's Handbuch der Biochemie der Menschen und der Tiere, 1910, iii, Part 1, 294.
40. Hirschstein: Med. Klin., 1914, x, 1569.

phorus, the sulphur excretion being especially high. Another type, designated plethoric hypothyroidism, is recognized by a high body resistance, the tissues showing no tendency to disintegration. Hirschstein determines by a preliminary trial which type predominates by thyroid feeding, or first by a high potassium diet, which he claims will cause a similar high excretion of sulphur, phosphorus, and nitrogen in the asthenic type, just as thyroid feeding does. He states that thyroid treatment in such patients is not advisable. The question arose whether these excreted end-products of protein metabolism were the results of tissue destruction or the washing out of residues stored in the body. The high sulphur and phosphorus excretion in some patients of the asthenic type, with great bodily wasting and susceptibility to intercurrent disease (tuberculosis), led him to believe that protein catabolism was the main factor. This author believes, however, that both forms are possible.

This study was carried out on a patient in the Jefferson Hospital, in the service of Dr. McCrae, to whom we are indebted for permission to study the case and for the clinical history, which is here given in part:

Clinical History.—Mrs. G. D., aged 28, white, was admitted to the Jefferson Hospital Aug. 6, 1913. Her general health had always been good. Menstruation was established at the age of 11 and was apparently normal in every respect until two years previous to her entrance it began to lessen in amount and duration. The previous year and one-half there had been amenorrhea. She had never been nervous until the onset of the present trouble. Her appetite always had been good, but for the previous four weeks it had been almost insatiable. The craving was mostly for bread and pastry. The bowels were regular. The present trouble began two years before. She noticed that her disposition had changed from an agreeable one to one markedly less so, that her temper flared up and she became irritated on the slightest provocation. These were the only symptoms apparent except for the beginning change in menstrual periods. Shortly afterward she noted a tremor of the hands, which had increased very little up to that time. In the previous year she noted that her eyes were becoming more prominent and in the previous three months she had noticed an increased size of her neck. On noticing this last symptom she consulted a physician, who treated her medically over a period of five weeks, with but slight improvement. During the medical treatment the patient received on three occasions hypodermic injections of pituitary extract and eight or nine days after each injection she became unconscious for periods of from twenty-four to seventy-two hours. She had headaches frequently and edema of ankles at times. She complained of dyspnea on slight exertion, but there was no dysphagia. In the previous six months the patient had gained considerable in body weight. Alopecia was noted of the hairy portions of the body. The patient was well nourished, with a most noticeable exophthalmos. The pulse was 110, the temperature 98.

Physical examination showed that on the neck there was an asymmetric enlargement of thyroid gland, more marked on the right than the left side. The enlargement began in the right side glands. There was no palpable thrill. The enlargement moves up on swallowing. The greatest circumference over the gland was 14¾ inches. The chest, lungs and heart sounds were normal. The

extremities were negative. The abdominal wall contained excessive amounts of fat.

The urinary examination was negative.

Blood examination on Aug. 15, 1913, showed hemoglobin 60 per cent., white cells 8,200, red cells 4,150,000, and color index 0.7 plus; the polymorphonuclears were 48 per cent., small lymphocytes 42 per cent., large lymphocytes 8 per cent., eosinophils 2 per cent. There was no reduced tolerance for glucose or fructose noted.

August 23 we began giving three lutein tablets daily to the patient. Bulimia continued. Examination of feces August 25 was negative. Wassermann examination resulted in positive three plus on September 5. On September 10, after mixed treatment, the patient showed a gain of 10 pounds the previous week. On the 11th she was given Roentgen-ray and thyroid treatment. On the 13th she was given pituitary treatment. On the 15th she was given 0.6 gm. salvarsan intravenously with no ill effects. On the 16th the weight indicated a loss of 6 pounds in the previous week. The patient stated that after the intravenous injection of salvarsan she felt a great deal more active mentally.

Blood examination, October 12, showed hemoglobin 91 per cent., red cells 5,950,000, color index 0.8, white cells 12,600.

An eye report of Aug. 11, 1913, showed vision of right eye 20/100, of left eye 20/200. The pupil diameter was 3.5 mm. The reactions to light, accommodation and convergence were normal. The muscle balance was normal, ocular movements were unimpaired, and the tension was normal. The eyeballs had undergone a proptosis of about 4 mm. in advance of the superior margin of the orbits. There was marked exophthalmos, so that the palpebral fissure could not be closed. Von Graefe's sign was present, as was also Stellwag's sign. Moebius' sign was absent. The right eye disk margins were clear and the vessels normal. There were no hemorrhages, and the fundus was negative. There was myopia of one-third diopter. The left eye mediums were clear, the disk margins were hazy on the nasal side, the cup was filled in, and the vessels were normal. The disk was slightly pale on the temporal side, and there was low myopia. The poor vision was due to the myopic condition of the eyes.

Roentgen examination on Aug. 13, 1913, showed the sella turcica and accessory sinuses normal. There was a calcareous deposit in the pineal gland.

The provisional diagnosis was goiter and pluriglandular disturbance.

PLAN AND METHOD OF STUDY

The patient was kept in a room in the Jefferson Hospital and under charge of a special nurse throughout the period of study. The purpose was to study the metabolism of the patient on a constant moderately high calcium diet, 1 gm., and to determine also the effect of the administration of both the thyroid and thymus gland substance. Both income and outgo of nitrogen, phosphorus, sulphur, calcium and magnesium were determined. The uniform diet and the amounts of each food given were based on the patient's choice during a preliminary day. The patient in all periods was placed on this uniform diet, which consisted of the foods given in Table 1, in addition 1 gm. of pure salt and 15 gm. of granulated sugar. There were also given each day bananas (scraped), 100 gm.; peaches (no juice), 100 gm.; tomatoes, 100 gm.; corn, 100 gm.; grape nuts, 50 gm.; potatoes (chips), 50 gm.; coffee, 200 c.c. and tea, 400 c.c.; both sampled daily. In order to reduce errors of sampling to a minimum, these foods were selected because of

the fact that they were low in calcium and nitrogen and yet gave variety to the diet. The details of food preparation and collection of excreta were carried out with the careful cooperation of the patient and of the hospital staff. The meat was prepared previous to the experiment, thoroughly mixed, boiled, and again thoroughly mixed, placed in glass jars, sterilized and kept in a frozen condition until used. Aliquot portions were taken for analysis.

TABLE 1.—Analysis of Foods†

Sample	Daily Food Intake	Sample No.	N	P_2O_5	MgO	CaO	S
Milk	100 c.c.	1	0.568	.....	0.023	0 15	.....
Milk	100 c.c.	2	0.568	Comp.	0.023	0.159	.....
Milk	100 c.c.	3	0.568	0.219	0.024	0.157	Comp.
Milk	100 c.c.	4	0.523	.....	0.025	0.162	0.025
Milk	100 c.c.	5	0.569	.....	0.025	0.163	.....
Cheese	50 gm.	1	2.064	.....	0.032	0.504	Comp.
Cheese	50 gm.	2	2.136	Comp.	0.033	0.529	.....
Cheese	50 gm.	3	2.272	0.621	0.03	0.486	Comp.
Cheese	50 gm.	4	2.3	.....	0.03	0.463	0.081
Cheese	50 gm.	5	2.44	.....	0.027	0.479	.....
Butter	50 gm. and 200 gm.	2	2.546	0.509	0.031	0.129	0.07
Bread							
Composite‡	.....	5	2.584	0.903	0.388	0.188	0.585
Meat (a)	100 gm.	3a	1.266	0.521	0.037	0.022	Comp.
Meat (b)	90 gm.	3b	1.203	0.475	0.037	0.026	0.102
City water	2,600 c.c.	...	.....	.....	0.04	0.035	0.029

* The milk and cheese were sampled and aliquot parts taken daily for period composites. Aliquot parts were again taken of these milk and cheese samples and composited into one sample each for both phosphorus and sulphur determinations. Aliquot parts of bread and butter were taken, which were composited into one sample. Patient began using meat 3b on Sept. 17, 1915. Proportionate aliquot parts of 3a and 3b were taken for sulphur, and for phosphorus in period 3.

† The daily intake consisted of (a) bananas (scraped), 100 gm.; peaches (no juice), 100 gm.; tomatoes, 100 gm.; corn, 100 gm.; (b) grape nuts, 50 gm.; potato chips, 50 gm.; (c) coffee, 200 c.c.; tea, 400 c.c. (tea and coffee sampled daily and aliquots taken). Portions (a) and (c) were evaporated to dryness and composited with (b) comprising Composite 5.

‡ The quantities given are the total daily intake in grams.

The investigation extended over twenty-six days and consisted of five periods of five days' duration, except Period 1, which consisted of six days.

Urine was collected in exact twenty-four hour samples and kept in a refrigerator. Thymol was used as a preservative. The feces were separated by the use of carmin and kept in thymolized friction-top cans in a frozen condition until the end of the period, when they were thoroughly mixed for analysis.

All of the calcium except that in the urine was determined gravimetrically by McCrudden's methods.[41] Urinary calcium was determined volumetrically by the same method. Nitrogen in the urine was estimated by the Kjeldahl-Gunning method. Phosphorus was determined by Neumann's method, gravimetrically. Sulphur in the urine was estimated by Benedict's method; in the food and feces, by a modification of Wolf and Osterberg's method.[42] The analytical data of foods, urine and feces are given in Tables 1, 2 and 3.

The periods into which the experiment was divided were: 1, a foreperiod, without any treatment; 2, a thyroid period, in which 6 grains of thyroid (Armour) were given daily, being increased to 9 grains each for the last two days, amounting to 36 grains in all; Period 3, a middle or after-period, in which no treatment was given; a thymus period

TABLE 2.—ANALYSIS OF FECES.*

Period Number	Feces	N	P_2O_5	MgO	CaO	S	Data
Foreperiod 1.....	443.5	9.49	4.981	1.393	5.084	0.563	Calculated to 5 day basis
Thyroid period 2.....	475.6	10.02	4.442	1.341	4.304	0.504	
Middle period 3.....	508.6	8.93	3.976	1.284	3.772	0.822	
Thymus period 4.....	521.1	9.64	4.328	1.345	3.871	0.745	
After period 5.....	544.5	9.16	4.116	1.242	3.91	0.808	Feces 5 of more liquid consistency

* The quantities given are the totals in grams for the respective periods.

(Period 4), in which 15 grains of thymus (Armour) were given daily, making a total of 75 grains, and an after-period (5), in which no treatment was given.

COMMENT

Some outstanding facts with regard to the metabolism in each of the periods of treatment will be outlined before going into a general discussion and comparison of the findings with regard to the individual elements concerned.

The point to be observed in Period 1, Table 4, with the patient receiving no treatment, is the loss of nitrogen, phosphorus, and magnesium, while calcium and sulphur are practically at a balance. The high daily loss of nitrogen amounts to 3.8 gm., or 37.03 per cent. of the intake. There is considerable loss of phosphorus, 0.399 gm., or 14.4 per cent. of the intake, while the loss of magnesium amounts to 0.025 gm., or 4.92 per cent.

41. McCrudden: Jour. Biol. Chem., 1910, vii, 83.
42. Wolf and Osterberg: Biochem. Ztschr., 1910, xxix, 429.

The calcium oxid and sulphur retentions announced to 0.01 and 0.023 gm., respectively. In this patient there was a loss of nitrogen somewhat over half as great as the gain Scholz[1] found in the case of his patient with goiter, who stored 7.437 gm. nitrogen daily without

TABLE 3.—ANALYSIS OF URINE *

Urine Number	Date	Vol., C.c.	N	P_2O_5	MgO	CaO	S
Foreperiod 1 (no treatment)							
1	9/ 3	910	8.1	1.448	0.171	0.017	0.581
2	9/ 4	2,265	15.08	3.02	0.313	0.016	0.967
3	9/ 5	2,210	9.98	1.659	0.228	0.009	0.544
4	9/ 6	Lost					
5	9/ 7	2,137	10.25	2.14	0.271	0.024	0.675
6	9/ 8	3,374	15.58	2.614	0.295	0.013	0.983
Period 2, thyroid treatment							
7	9/ 9	2,980	13.2	2.319	0.26	0.024	0.77
8	9/10	2,131	7.92	1.323	0.152	0.016	0.472
9	9/11	2,825	9.81	1.91	0.189	0.017	0.696
10	9/12	2,521	13.1	2.466	0.269	0.023	0.828
11	9/13	1,896	7.64	1.318	0.139	0.016	0.476
Period 3 (no treatment)							
12	9/14	2,200	6.8	1.393	0.127	0.006	0.675
13	9/15	1,615	6.42	1.142	0.101	0.018	0.466
14	9/16	1,800	7.9	1.37	0.139	0.018	0.52
15	9/17	1,948	10.76	1.715	0.218	0.024	0.742
16	9/18	1,535	8.16	1.044	0.159	0.023	0.715
Period 4, thymus treatment							
17	9/19	865	6.6	0.868	0.147	0.015	0.609
18	9/20	1,800	8.53	1.16	0.168	0.018	0.79
19	9/21	1,210	6.14	0.95	0.119	0.007	0.434
20	9/22	1,030	7.22	1.27	0.154	0.01	0.562
21	9/23	1,212	10.28	1.609	0.214	0.013	0.748
Period 5 (no treatment)							
22	9/24	1,610	8.06	1.456	0.181	0.018	0.565
23	9/25	1,975	7.7	1.132	0.174	0.016	0.633
24	9/26	1,735	6.82	0.906	0.14	0.015	0.455
25	9/27	2,168	7.53	1.065	0.186	0.029	0.498
26	9/28	1,310	6.53	0.982	0.144	0.013	0.43

* The quantities given are the totals in grams for each day.

treatment. The opposite condition obtains here. That sulphur is not lost with such a high daily excretion of nitrogen is unusual Vermehren[24] observed in myxedema a loss of 20 per cent. of nitrogen by

the feces, and Anderson[43] observed defective absorption as regards nitrogen and fat. In such cases the absorption improves with thyroid treatment.[19] Improved absorption from the intestine was observed in Period 2 (Table 5) after thyroid administration. The urinary calcium excretion is unusually low, 15.9 mg. in twenty-four hours, or 1.54 per

TABLE 4.—Period 1; Balance of Nitrogen, Phosphorus, Magnesium, Calcium and Sulphur *

	N	P_2O_5	MgO	CaO	S
Excretion, urine	11.8	2.176	0.256	0.016	0.752
Excretion, feces	2.28	0.996	0.279	1.006	0.117
Excretion, total	14.08	3.172	0.534	1.023	0.869
Ingestion, total	10.27	2.773	0.509	1.032	0.892
Retention or loss	−3.8	−0.399	−0.025	+0.01	+0.023
Per cent. of retention or loss	−37.03	−14.40	−4.92	+0.94	+2.57

* The quantities given are daily averages in grams.

cent., while the calcium in the feces is high, 97.8 per cent. of the total intake. Nitrogen in the feces was approximately three times the normal, being 22.2 per cent., indicating poor absorption. The condition of metabolism here, with high urinary losses, is such that there was a considerable amount of work for the kidneys to perform. The metabolism was below normal. The patient's weight remained constant at

TABLE 5.—Period 2, Thyroid Treatment; Balance of Nitrogen, Phosphorus, Magnesium, Calcium and Sulphur *

	N	P_2O_5	MgO	CaO	S
Excretion, urine	10.31	1.868	0.201	0.019	0.652
Excretion, feces	2	0.889	0.268	0.861	0.119
Excretion, total	12.32	2.756	0.57	0.88	0.771
Ingestion, total	10.1	2.773	0.502	1.062	0.892
Retention or loss	−2.22	0.017	0.032	0.182	0.121
Per cent. of retention or loss	−21.96	0.61	6.36	17.1	13.56

* The quantities given are daily averages in grams.

183 pounds, when not under medication. On August 24 her weight was 181 pounds, and on September 7 it was 183, indicating a gain of two pounds with metabolism below normal.

In Period 2, Table 5, 36 grains of thyroid gland, ingested in five

43. Anderson: Hygiea, 1898, lx, 68; Jahresb. ü. d. Fortschr. d. Thierchem., 1899, xxix, 427.

days, produced a marked effect on metabolism, causing a distinct increased retention over Period 1 of 15.07 per cent. nitrogen, 15.01 per cent. phosphorus pentoxid, 10.78 per cent. magnesium oxid, 16.16 per cent. calcium oxid and 10.99 per cent. sulphur. Nitrogen alone of all these elements remains negative at 21.96 per cent., or a daily loss of 2.22 gm. This agrees with Magnus-Levy's[19] finding in myxedema.

Sulphur metabolism need not always parallel that of nitrogen. Magnus-Levy found the losses were greater during the beginning of the treatment. The nitrogen losses during the first nine days of his investigation were, respectively, 1.1, 0.3, 1, 2.7, 1.8, 3.3, 2.9, 1.6, and 2.9 gm., averaging 1.96 gm. The great daily variation in nitrogen losses is noticeable in the present instance. Phosphorus retention is 0.017 gm., or 0.61 per cent., being almost a balance. In case of calcium and sulphur there was a decided retention, amounting to 0.182 gm. and 0.121 gm., respectively, indicating for calcium, at least, a better absorption from the intestine. The same fact holds for nitrogen and calcium in the feces, which are 19.8 and 81.27 per cent., compared to 22.2 and 97.8 per cent., respectively, in Period 1. There was practically no change in calcium oxid excreted through the kidneys. The body weight now decreased to 177 pounds on September 17, which represented a considerable loss (at least six pounds) after the experiment began. While the volume of urine excreted in Period 1 was high, there now was an average increase of 293 c.c. (diuresis) (Table 3). This will be discussed more fully later. Incomplete data indicate that thyroid also increased the sodium chlorid excretion.

TABLE 6.—Period 3, Postthyroid Period; Balance of Nitrogen, Phosphorus, Magnesium, Calcium and Sulphur *

	N	P_2O_5	MgO	CaO	S
Excretion, urine	8.01	1.333	0.149	0.018	0.629
Excretion, feces	1.79	0.795	0.257	0.754	0.164
Excretion, total	9.80	2.128	0.406	0.773	0.793
Ingestion, total	10.25	2.770	0.5	1.021	0.892
Retention or loss	0.45	0.642	0.094	0.248	0.099
Per cent. of retention or loss	4.39	23.17	18.77	24.33	11.06

* The quantities given are daily averages in grams.

The nitrogen balance in Period 3 shows a retention of 0.48 gm., or 4.39 per cent. This indicates an increased retention of 26.35 per cent. over the preceding period. The stimulating effect of thyroid on metabolism continues and is greater in this than in the thyroid period. This is also true of phosphorus, in which the retention reached 23.7

per cent. The magnesium retention increased over the preceding period to 18.77 per cent.

The increase of calcium and sulphur was less in this period than in the preceding. However, magnesium and calcium in this period reach the maximum retention of 18.77 and 24.83 per cent., respectively, or 0.098 and 0.248 gm. This leaves 73.7 per cent. calcium oxid excreted through the feces, which in Period 1 contained 97.8 per cent. Urinary calcium does not vary any more than 0.55 per cent., or a mean of 7 mg. per day throughout the investigation. In this period, five to ten days following thyroid treatment, it is seen that the thyroid exerts its greatest effect on the metabolism of calcium and magnesium, which reaches its maximum quicker than metabolism of the other elements. The sulphur retention of 11.06 per cent. showed a slight decrease. Fifteen grains of thymus were administered daily, or a total of 75 grains for a period of five days.

TABLE 7.—PERIOD 4; EFFECT OF THYMUS TREATMENT ON NITROGEN, PHOSPHORUS, MAGNESIUM, CALCIUM AND SULPHUR RETENTION *

	N	P_2O_5	MgO	CaO	S
Excretion, urine	7.75	1.171	0.161	0.013	0.619
Excretion, feces	1.93	0.866	0.269	0.776	0.149
Excretion, total	9.68	2.037	0.43	0.789	0.768
Ingestion, total	10.32	2.727	0.502	1.002	0.892
Retention or loss	0.63	0.69	0.072	0.216	0.124
Per cent. of retention or loss	6.15	25.3	14.31	21.5	13.85

* The quantities given are daily averages in grams.

The metabolism in Period 3 shows a retention of all elements, nitrogen being the lowest, 4.39 per cent. On administration of thymus gland (Period 4) the retention of nitrogen increases slightly, 1.76 per cent., or to 0.634 gm.; there was also a slightly increased retention of phosphorus and sulphur. However, magnesium oxid and calcium oxid retention decreased by 4.46 per cent. and 2.83 per cent., or the retention was 14.31 and 21.50 gm., respectively. The continuing effect of thyroid is not apparent in the magnesium and calcium metabolism; but this effect is shown in the slight increases in the metabolism of nitrogen, phosphorus and sulphur. That this is the lagging effect of thyroid stimulation, rather than the effect of thymus, appears probable. Blondel, as well as Tarrulli and Curatulo[44] claim that feeding of thymus causes increased nitrogen and phosphorus excretion.

44. Blondel, Tarulli and Curatulo: Biedl's Innere Sekretion, 1913, Part 1, 303.

In general, the results with thymus feeding have been negative. The urine excretion during this period decreased markedly to a daily mean of 1,239 c.c. The body weight of the patient also decreased 8 pounds from September 17 to the 24th, even though there was retention of all the elements, which is greatest relatively for phosphorus and calcium, being 25.30 and 21.50 per cent. respectively.

TABLE 8.—Period 5; Balance of Nitrogen, Phosphorus, Sulphur, Calcium and Magnesium in the Postthymus Period

	N	P_2O_5	MgO	CaO	S
Excretion, urine	7.33	1.106	0.165	0.018	0.520
Excretion, feces	1.83	0.823	0.248	0.782	0.162
Excretion, total	9.16	1.981	0.414	0.8	0.682
Ingestion, total	10.46	2.727	0.498	1.019	0.892
Retention or loss	1.3	0.796	0.085	0.219	0.21
Per cent. of retention or loss	12.45	29.19	16.96	21.47	23.56

* The quantities given are daily averages in grams.

TABLE 9.—Retention or Loss, Percentage

	1	2	3	4	5
N	—37.03	—21.96	4.39	6.15	12.45
P_2O_5	—14.4	0.61	23.17	25.3	29.19
MgO	—4.82	6.36	18.77	14.31	16.96
CaO	0.94	17.1	24.33	21.5	21.47
S	2.57	13.56	11.06	13.85	23.56

TABLE 10.—Retention or Loss, Absolute, in Grams

	1	2	3	4	5
N	—2.80	—2.22	0.45	0.62	1.3
P_2O_5	—0.390	0.017	0.642	0.69	0.796
MgO	—0.065	0.032	0.094	0.072	0.085
CaO	0.01	0.182	0.248	0.216	0.219
S	0.023	0.121	0.099	0.124	0.21

In the postthymus period (Period 5) the retentions of the elements remained high, being at a maximum for the elements nitrogen, phosphorus and sulphur.

Tables 9 and 10 give the absolute and percentage retentions for all periods. It will be seen that the great increases in retention occurred

toward the left of the table, that is during the thyroid period (Period 2) or in the postthyroid period (Period 3). The increases in retention after Period 3 are gradual for all elements.

On the whole the retentions, both relative and absolute, are at their maximum in the postthymus period, sulphur 23.56 per cent., phosphorus 29.19 per cent., calcium 21.47 per cent., magnesium 16.96 per cent. (calcium and magnesium were highest in Period 3, 24.33 per cent. and 18.77 per cent., respectively), nitrogen 12.45 per cent. The absolute retentions occurred in the following order: nitrogen 1.3 gm., calcium 0.219 gm., sulphur 0.21 gm., phosphorus 0.796 gm., magnesium 0.085 gm. The percentage of retentions show there is a certain parallelism in metabolism for nitrogen and the mineral elements. Towles,[45] studying metabolism in exophthalmic goiter, has pointed out that there is often a parallelism between the nitrogen and calcium in health and disease, unless the calcium intake is very high. McCrudden and Fales[46] point out that this has been found for other elements, and that it holds for the retention of nitrogen and of the mineral elements in a normal body. Hoffström,[47] who studied the metabolism of a pregnant woman over a long period, also showed a similar retention of nitrogen and the other elements.

It will be noted that the maximum retentions of nitrogen, phosphorus and sulphur occurred in the final period, while the highest retentions for calcium and magnesium occurred in the postthyroid period; that is, with calcium and magnesium the maximum effects were reached earlier.

With regard to the influence of thymus administration, it will be noted that when this treatment was discontinued, there is a rise in retention in the case of all elements. Furthermore, in the cases in which the rise in retention is continuous, the retention increased to a greater extent when thymus was withdrawn than it had in the preceding period. That is, the thymus treatment apparently produced an effect distinguishable from and opposed to the continuing effect of the thyroid treatment. It appears to have exerted a depressing effect on the thyroid stimulation of metabolism. In view of the lack of data with regard to the effect of thymus administration on metabolism, the interpretation of these findings offers many difficulties. Falta,[48] on the basis of indirect evidence, suggests that probably the thymus gland belongs to the anabolic (retardative) group of ductless glands, as contrasted with the thyroid as a member of the catabolic or dissimilatory group.

45. Towles: Am. Jour. Med. Sc., 1910, cxl, 100.
46. McCrudden and Fales: THE ARCHIVES INT. MED., 1912, ix, 273.
47. Hoffström: Skand. Arch. f. Physiol., 1910, xxiii, 326.
48. Falta, Bolaffio, and Tedesco: Cited by Biedl (65) Part 1, p. 164. Falta and Meyers: The Ductless Glandular Diseases, Philadelphia, 1915, p. 80.

Through the pioneer work of Hertoghe it has been shown clinically how frequently hypothyroidism occurs, causing various slight infiltrations now clinically recognized and relieved by thyroid medication.

Our knowledge of the purpose of the thymus gland in metabolism is obscure. However, in the last few years the observations of surgeons have added considerably to our knowledge. Swale Vincent[49] observes that the conception that the thymus is not altogether a lymph organ is gaining ground. A nutritive rôle has also been suggested for the thymus, it being a glandular organ rich in nucleoprotein.

Weil,[50] Hart and Nordmann,[51] state that on the whole the verdict appears to be that the organ is not essential to life, even in quite young animals. It has long been thought that the human thymus reaches its greatest development at about the second year, and then begins to degenerate. But it was shown in the year 1890 by Waldeyer[52] that even in advanced age a considerable amount of thymus tissue persists and probably maintains its function as does the thyroid. Zoja[53] had previously shown that the thymus persists till the age of puberty. Recently Hammar[54] has insisted that the organ continues to grow up to the period of puberty, and reaches its greatest development between the fourteenth and sixteenth years. Microscopic evidence shows that it functions still later, though losing in weight. A true atrophy of the parenchyma, with elimination of function, comes on at about 50 or 60 years of age. At this period the thyroid function also decreases (Hertoghe). It seems, then, that we must regard the thymus as an organ regularly present, and probably in an active functional condition up to the age of puberty, if not up to the menopause.

Gare and Capelle hold there is a reciprocal relation between the thyroid and thymus glands. The association between the thyroid and thymus glands[55] may be of importance in hyperthyroidism, in which a hyperplasia of the thymus has been reported to occur. Indeed, the degree of the latter has been directly related to the severity of exophthalmic goiter manifestations.[56] H. Matti reports that research and study of the literature show thymus with thyroid are directly concerned with the production of exophthalmic goiter. Thymus changes are directly coordinate with and parallel to changes in the thyroid.[57]

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49. Vincent: Internal Secretion and the Ductless Glands, London, 1912.
50. Weil: Lyon Med., 1910, cxv, 847.
51. Hart and Nordmann: Berl. klin. Wchnschr., 1910, xlvi, 814.
52. Waldeyer: Verhandl. des 10 Internat. Med. Cong., Berlin, 1891, p. 15; cited by Vincent (Footnote 49) p. 357.
53. Zoja: Cited by Vincent (Footnote 49), p. 358.
54. Hammar: Verhandl. d. Anat. Gesellsch. a. d. 19te Versammlung, Geneva, 1905.
55. Hoskins: Am. Jour. Med. Sc., 1911, cxli, 1349.
56. Gebele: Beitr. z. klin. Chir., 1910, lxx, 20.
57. Matti: Berl. klin. Wchnschr., 1914, li, 1365.

Tatum found that the thymus of rabbits atrophied after excision of the thyroid. A. Kocher[58] states that a tendency to tardy hyperplasia or tardy involution of the thymus is evident in nearly 50 per cent. of all cases of exophthalmic goiter. Halsted[59] in exophthalmic goiter twice found the thymus enlarged, with typical thymus symptoms predominating, and also found that 82 per cent. of the postmortem examinations showed thymus enlargement, while in those deaths due to heart failure after operation 95 per cent. showed thymus enlargement.[60] Gebele[61] describes persistent thymus in exophthalmic goiter. The castration experiments of Marassini and Gellin[62] point out that this operation gives rise to an enlargement of the thymus, and Squandrini[62] believes that castration interferes with the normal involution of the gland. These experiments further point to some kind of internal secretion which ministers to the economy of the organism before the reproductive organs are fully developed. They believe that normally this internal secretion is provided by the testes or ovary after puberty, but if castration is perfected the thymus maintains its original structure and function.

Defective nutrition is caused in young dogs by extirpation of the thymus, the animals usually living about a year. Again, dilatation of the heart in such animals suggested that the thymus has an antagonistic action to the suprarenals.[49] The fatal effects of thymectomy in rats, as found by Klose and Marquini, could not be confirmed by Pappenheimer,[63] using controls of the same litter.

Soli[64] found changes in the development of bone in animals deprived of their thymus (supposedly deranged metabolism). Rabbits, if deprived of their thymus at a sufficiently early stage in their development, fail to develop their bony skeleton normally, while guinea-pigs and chickens respond less readily. Utterström,[65] after feeding thyroid to rabbits for weeks and months, concluded that two factors in hyperthyroidism affect the thymus: one is an indirect depressing effect, due to a disturbance in metabolism; the other is a direct stimulation, due to hyperthyroidism. Which predominates depends on the animal's constitution, conditions of the experiment and especially on the size of the thyroid dose.

58. Kocher: Arch. f. klin. Chir., 1914, cv, 769, 832.
59. Halsted: Bull. Johns Hopkins Hosp., 1914, xxv, 223.
60. Falta and Meyers in The Ductless Glandular Diseases, p. 45, say: "That long continued oversaturation of the body with the thyroid gland secretion may give rise to disturbances of the functions of the sexual glands is not at all remarkable, only the significance of the thymus hyperplasia is as yet unclear."
61. Gebele: Beitr. z. klin. Chir., 1910, [illegible] 20.
62. Marassini, Gellin and Squandrini: Cited by Vincent (Footnote 49), p. 365.
63. Pappenheimer: Jour. Exper. Med., 1914, xix, 319.
64. Soli: Arch. ital. biol., 1909, lii, 217; Chem. Abstr., 1911, v, 2128.
65. Utterström: Arch. de méd. exper. et d'anat. path., 1910, xxii, 550.

DIURESIS

A marked daily increase in urine volume (average volume 2,472 c.c.) occurred during thyroid treatment over that of the foreperiod (Period 1) (average volume 2,179 c.c.), which increase amounted to 293 c.c. The patient was on a constant water intake. The urine volume of Period 2 also exceeded that of the following period by 652 c.c. As shown by Rahel Hirsch (Table 13), in the work of Scholz,

TABLE 11.—Diuresis Due to Thyroid Treatment *

Period		Mean Temperature, F.	Mean Urine Volume, C.c.
No treatment	1	70.7	2,179
Thyroid	2	59.8	2,472
No treatment	3	67.0	1,820
Thymus	4	75.6	1,239
No treatment	5	61.2	1,759

* Period averages are given.

Richter and Bürger, there is a marked increased excretion of urine by persons on thyroid administration, except in the case of Gluzinski and Lemberger, in which there was a decrease. Scholz obtained an increase of 886 c.c.; Richter 219 c.c.; Bürger 122 c.c.; while Gluzinski and Lemberger obtained a decrease of 206 c.c. In our experiments, during thymus treatment the volume went down to 1,239 c.c., or 1,233 c.c. less than with thyroid, a variation of almost 100 per cent. While

TABLE 12.—Urine Volume Does Not Vary with Temperature

Period	Temp., F.	Urine Vol., C.c.
2	59.8	2,472
5	61.2	1,759
3	67.0	1,820
1	70.7	2,179
4	75.6	1,239

the greatest and lowest volume of urine occurred when the temperature was lowest, 59.8 F., and the highest 75.6 F., respectively, yet a variation of 1,233 c.c. of urine is considerable in a hospital in which temperatures are more constant and normal. Rearranging the urine volumes according to increase in temperature (Table 12) shows that the volume varies independently of temperature. Pointing out one instance will suffice. During the second warmest period (Period 1) the urine volume was

2,179 c.c., while in the warmest period (Period 4) this was 1,239 c.c. Magnus-Levy found that the urine increased somewhat during thyroid treatment in myxedema (hypothyroidism) on constant water intake. This, he says, is supposedly due to the disappearance of watery myxedematous deposit and other substances, and that the same holds for thyroid extract administered to the nonmyxedematous.

TABLE 13.—URINE VOLUME, QUOTED FROM RAHEL HIRSCH (OPPENHEIMER) *

C.c. Urine, Foreperiod	Author	C.c. Urine, Treatment Period
2,396	Scholz	3,282
1,120	Richter	1,339
1,419	Gluzinski and Lemberger	1,213
1,044	Bürger	1,166

* Oppenheimer: Handbuch der Biochemie, 1910, iii, Part 1, 294.

Friedleben[66] noticed diminished urine volume, decrease in amount of urea, increased appetite and that the metabolism was altered in thymectomized animals. During the thymus period in the case under investigation the volume of urine decreased to 1,239 c.c., and in the following period again rose to 1,759 c.c. (Table 11). Whether this marked decrease in volume is due to thymus ingested or is a coincidence has not been definitely determined.

TABLE 14.—VARIATION IN BODY WEIGHT

Date	Period	Weight, Pounds	Change, Pounds
8/24/14	...	181	
9/ 7/14	1	183	Gain 2
9/17/14	3	177	Lost 6
9/24/14	4, end	185	Gain 8
10/ 2/14	End of Exp.	174	Lost 11
5/15/15	...	183	
	Before illness	165	
7/17/16	...	185.5	

Various results had been obtained with thymus extract prepared in different ways. Gouin and Audouard[67] report increased activity of the kidney by using subcutaneous injection of glycerol extracts of thymus glands.

66. Friedleben: Cited from Oppenheimer's Handbuch der Biochemie, 1910, iii, Part 1, 335.

67. Gouin and Audouard: Biedl's Innere Sekretion, 1913, Ed. 2, Part 1, 302.

An outstanding fact in this case is the marked variation in body weight. The weights during the present investigation for the periods given are as shown in Table 14.

From August 24 to September 7 the patient gained two pounds in weight. Previous to September 1 the patient had been on thymus treatment. The clinical data indicate a slight edema on September 1: "Areas of thickening in the subcutaneous tissues. With these thickened areas there appeared a sense of constriction over upper chest and fugitive pains generally distributed." The kidneys at this time were eliminating large quantities of nitrogen (3.8 gm.) in excess of ingestion and also large amounts of water. With imperfect elimination of nitrogenous end-products from the tissues, due to poor or decreased oxidation, it is easily conceivable that there could occur a slight edema or myxedema, with retention of some water, and hence a slight increase in weight.

Thyroid treatment, however, caused increased water excretion and with its stimulating effect on metabolism brought about retention of other constituents. The loss in weight (6 pounds) is perhaps due chiefly to water. We can approximately calculate this from nitrogen loss and water excretions from September 7 to 17 (Table 14). During this period there was a loss of 6 pounds in body weight. The total loss of nitrogen from September 7 to 14 amounted to 22.5 gm. This, calculated to the basis of tissue equivalent (6.25 and 4.7, protein and tissue factors), gives 1.5 pounds tissue loss. Diuresis of 293 c.c. daily for five days (excess in Period 2 over Period 1) causes a loss of 1,465 c.c. This amounts to 1,487 gm., or 3.3 pounds (specific gravity 1.015). The loss of 3.3 pounds water with 1.5 pounds tissue loss accounts for 4.8 pounds. The actual loss was 6 pounds.

In Period 4 there is a distinct retention of all the elements, especially nitrogen. Urine excretion decreases in volume and gain in weight occurs. In our case this amounted to 8 pounds. This continues through the thymus period. Thymus may also cause a retention of water. The above gain occurred from September 17 to 24.

This gain in weight due to retention of nitrogen and of water can approximately be calculated from the urine volumes. The nitrogen retention in Period 3 was 0.45 gm. daily; that is, 0.90 gm. of nitrogen was retained up to September 19. Retention of nitrogen for Period 4 was 0.634 gm. daily, or a total of 3.17 gm. The total nitrogen retention for September 17 to 24 was 4.07 gm., equivalent to 0.3 pound of tissue built up. The mean daily urine excreted is not so readily approximated, but averaging the volumes for Periods 3 and 5 gives 1,790 c.c., which can be taken as the average. For the thymus period there would be a retention of 551 c.c. a day, which totals 2,755 c.c., or 2,796 gm. This is equivalent to 6.2 pounds, and with the 0.3 pound

of tissue, gives 6.5 pounds gain for September 17 to 24. The actual gain was 8 pounds.

It has been held that the fat in this disorder is readily oxidizable and perhaps the loss of 11 pounds (from September 24 to October 2, Table 14) is due partly to such oxidation. Agreeing with this is the fact that little or no sulphur loss occurs during the periods of great nitrogen losses (Periods 1 and 2). Hirschstein[40] found the sulphur loss was extraordinarily high when great emaciation occurs in hypothyroidism.

The Chittenden low-protein diet allows 0.12 gm. nitrogen per kilogram of body weight, which Sivén was able to reduce to 0.08 gm. per kilogram. In our case the metabolism of nitrogen, as shown by the urinary nitrogen figured on the basis of kilograms of body weight, is low, indicating a low state of metabolism. Results on this basis are perhaps partly due to the presence of inactive adipose tissue. Table 15 illustrates this fact.

TABLE 15.—NITROGEN METABOLISM

Period	Weight		Mean N in Urine, Gm.	N per Kg. Body Weight, Gm.
	Lbs.	Kg.		
	165	74	11.8	0.16
1	183	83	11.8	0.14
4	185	84	7.32	0.09

The daily intake of 2,058 calories, corresponding to 25 calories per kilogram body weight, with choice of diet, also indicates a low energy metabolism.

NITROGEN METABOLISM

Table 16 points out the gradual decrease of nitrogen, absolute as well as relative, in the feces. Vermehren[24] observed in myxedema a loss of 20 per cent. of nitrogen by way of the feces and Anderson[43] observed defective absorption of nitrogen and fat, but states that with thyroid treatment absorption improved. The best absorption in our patient showed an improvement of 4.7 per cent. over Period 1. This occurred in the postthyroid period. The nitrogen in the urine decreased from 114.8 per cent. of the intake to 70.2 per cent., a difference of 44.6 per cent. There were less of the nitrogenous end-products given off and more nitrogen retained. Large increases in nitrogen retention occurred in Periods 3 and 5, following the thyroid and thymus periods, being respectively 26.35 and 6.30 per cent. The nitrogen metabolism went from a daily loss of 3.8 gm. to a retention of 5.1 gm., within a period of twenty-six days. The variation in nitrogen balance thus reached a maximum of 49.48 per cent. This increase in

nitrogen metabolism is further substantiated by the fact that the sulphur retention increased 20.99 per cent., phosphorus 43.59 per cent., while the mineral elements, calcium and magnesium, were retained in about the same amount as that of sulphur.

In the foreperiod and the thyroid period the nitrogen balance was negative, with a loss of 3.8 and 2.2 gm., respectively. Thyroid feeding stimulated nitrogen retention by 15 per cent., which increased to 26 per cent. in the postthyroid period (Period 3). There was a drop in the urinary excretion of nitrogen of 24 per cent., or 2.3 gm. This indicated increased retention. The nitrogen loss of 2.2 gm. changed in Period 3 to 0.05 gm. retention. This marked effect of nitrogen metabolism continues through the remaining periods. An interesting point to note is that the relative absorption through the intestine in both posttreatment periods (Periods 3 and 5) was the same, the absolute values for nitrogen in the feces being respectively 1.79 and 1.83 gm., a difference of 45 mg., while there was a difference of 0.22 gm. in the nitrogen ingested. Hence in these posttreatment periods it will be observed that the absorptive power of the intestine for nitrogen was not changed to any extent. This appears to hold also for sulphur and phosphorus (Tables 16, 19 and 22).

TABLE 16.—METABOLISM OF NITROGEN FOR ALL PERIODS (RELATIVE AND ABSOLUTE) *

	Grams N, for All Periods					Percentage Based on Intake, for All Periods				
	1	2	3	4	5	1	2	3	4	5
Ingestion	10.27	10.1	10.25	10.32	10.46	.....	.....	.....	.....	.....
In feces	2.28	2	1.79	1.93	1.83	22.2	19.8	17.4	18.6	17.5
In urine	11.8	10.31	8.01	7.75	7.33	114.8	102.2	78.2	75	70.2
Retention	—3.8	—2.22	0.45	0.63	1.3	—37.03	—21.99	4.39	6.15	12.45

* Maximum increased retention 49.48 per cent. (Period 5).

Daddi and Marchetti[28] found the utilization of nitrogen good in thyroid treatment of exophthalmic goiter, even though the stools were somewhat soft. We confirmed this on feces Composite 5, which were more liquid in consistency. Our data on the administration of thyroid confirm the observations of Magnus-Levy [19] that the gradual effect of thyroid action on the nitrogenous exchange, both in myxedematous and nonmyxedematous, and its persistence after the administration has been stopped, are very noticeable; that while there are differences in the degree of reaction of individuals, this reaction is no more noticeable for the obese than for other individuals. The loss of nitrogen in the feces remained high (from 22.2 to 17.4 per cent.), that is, the variation

in absorption was slight, 4.8 per cent. (Table 17). There is in general, however, a gradual decrease in fecal nitrogen, being 0.28 and 0.49 gm., respectively during the thyroid and postthyroid periods. Fecal nitrogen, in the thymus and postthymus periods, increased over Period 3 (forethymus period) by 0.14 and 0.24 gm., respectively.

Corresponding with the continued effect of thyroid on metabolism, the urinary nitrogen shows a gradual decreased elimination from 11.8 gm. (Period 1) to 7.33 gm. (Period 5), or a difference of 4.47 gm., amounting to 44.6 per cent. The nitrogen excretion during the thyroid and postthyroid periods was, respectively, 1.48 and 3.80 gm. less than in the foreperiod (Period 1); during the thymus and postthymus

TABLE 17.—Gradual Decrease of Nitrogen in Urine and Feces (Relative and Absolute)

Period	N Intake, Gm.	N in Urine, Gm.	N in Urine, per Cent.	N in Feces, Gm.	N in Feces, per Cent.
1	10.27	11.8	114.8	2.28	22.2
2	10.1	10.31	102.2	2	19.8
3	10.25	8.01	78.2	1.79	17.4
4	10.32	7.75	75	1.93	18.6
5	10.46	7.33	70.2	1.83	17.5

TABLE 18.—Maximum Variation in Absorption, Excretion and Retention

	Absorption	Excretion, Urine	Retention	Period
N	4.8	44.6	49.48	5
P_2O_5	7.3	37.9	43.59	5
MgO	5	20.6	23.69	3
S	5.2	26	20.99	5
CaO	24.1	0.57	22.20	3

periods, 4.05 and 4.47 gm. less than in Period 1, indicating that during both treatment with thyroid and thymus there was a more favorable nitrogen balance.

Table 18 is interesting because of several facts brought out. The variation in absorption from the intestine for all elements is fairly constant, approximating 5 per cent. Phosphorus runs slightly higher. Calcium, while constant in the urine, varies up to 24.1 per cent. in the feces and must be excreted by this channel. The retention of the other four constituents is indicated by the urine content. Table 18 shows that this exceeds 20 per cent. for all (except calcium being

greatest for nitrogen and phosphorus, respectively). It should be observed that the maximum increased retention was about the same for calcium and magnesium and occurred earlier (Period 3) than for the elements (nitrogen, phosphorus and sulphur) concerned in the metabolism of protein (Period 5), which was respectively 49.48, 43.59 and 20.99 per cent. Thus calcium and magnesium metabolism appear to be affected differently by thyroid stimulation than that of nitrogen, phosphorus and sulphur.

PHOSPHORUS METABOLISM

There was a fairly progressive decrease in the excretion of phosphorus by way of the intestines during and after thyroid treatment. The excretion of the feces during thymus feeding increased somewhat, as it also did for nitrogen. The lowest excretion in the feces occurred following thyroid action. In the next two periods, Periods 4 and 5,

TABLE 19.—METABOLISM OF PHOSPHORUS IN ALL PERIODS, RELATIVE AND ABSOLUTE AMOUNTS (PHOSPHORUS PENTOXID) *

	Phosphorus in All Periods, Gm.					Phosphorus in All Periods, per Cent.				
	1	2	3	4	5	1	2	3	4	5
Ingestion.....	2.773	2.773	2.770	2.727	2.727	.....	.....	.....	.....	.....
In feces.....	0.906	0.889	0.795	0.866	0.823	35.9	32.1	28.6	31.7	30.1
In urine.....	2.176	1.868	1.333	1.171	1.108	78.5	67.4	42.8	42.8	40.6
Loss or retention...	−0.290	0.017	0.642	0.69	0.796	−14.4	0.61	23.17	25.3	29.19

* Maximum retention 43.59 per cent. (Period 5).

there was a slight rise, but all variations were within the narrow limits of 7.3 per cent. Thus, it is seen that there was no marked increase in phosphorus metabolism with excretion through the bowel, such as Scholz[19] observed in his case.

The progressive decrease of phosphorus excretion in the urine is noticeable, being from 2.18 to 1.11 gm., or a difference of 1.07 gm. (40.6 per cent.). Thyroid action caused a decreased excretion of 0.31 gm. and thymus 0.16 gm. over the preceding period in each case. This extended also into the postthyroid and postthymus periods, being 0.54 gm. and 0.06 gm., respectively. The maximum retention was 43.59 per cent. in Period 5.

MAGNESIUM METABOLISM

There was not over 5 per cent. variation in absorption of magnesium oxid from the intestine. A variation from 54.8 (Period 1) to 49.8 (Period 5), per cent. occurred. The absorption from the feces during thyroid and thymus action was practically the same, differing

only by 0.3 per cent. A marked effect of treatment on magnesium metabolism is seen from the urinary data. Excretion of magnesium oxid varied in Period 1 from 0.256 gm. to 0.149 gm. (Period 3), or from 50.4 to 29.8 per cent. The lowest excretion is caused by the continuing thyroid stimulation. The greatest retention occurs here (18.77 per cent.). The excretion rises slightly in Period 4 during thymus administration and also in Period 5 (33.06 per cent.). The maximum retention occurs in Period 5 (16.96 per cent.). This is an increased retention after the experiment began of 23.69 per cent. The absolute values for magnesium oxid retention in any period are small, being less than 100 mg.

TABLE 20.—METABOLISM OF MAGNESIUM IN ALL PERIODS (RELATIVE AND ABSOLUTE) *

	As MgO, Gm.					As MgO, per Cent.				
	1	2	3	4	5	1	2	3	4	5
Ingestion	0.509	0.502	0.5	0.502	0.498	.....	.....	.....	.....	.....
In feces	0.279	0.268	0.257	0.269	0.248	54.8	53.4	51.4	53.7	49.8
In urine	0.256	0.202	0.149	0.161	0.165	50.4	40.3	29.8	32.04	33.06
Loss or retention	—0.025	0.032	0.094	0.072	0.085	—4.92	6.36	18.77	14.31	16.96

* Maximum retention 23.69 per cent. (Period 3).

CALCIUM METABOLISM

In the first two periods there is apparently a condition of depressed metabolism with loss of magnesium, phosphorus and nitrogen, calcium and sulphur being at a balance. The kidneys functionated but slightly in calcium metabolism, excreting 0.420 gm. in twenty-five days (from 12 to 18 mg. daily). This is less than 2 per cent. of the ingested calcium. Secchi[68] found for a man 70 years old that the lowest urinary excretion was 9.4 per cent. on a high calcium diet (3.65 gm. per day). The calcium eliminated in the foreperiod by way of the intestines in our patient was 97.7 per cent. of the intake.

During thyroid treatment absorption improved. Calcium oxid in the feces decreased to 81.2 per cent., or 0.146 gm. The least calcium oxid eliminated by way of the feces (73.7 per cent. or 0.754 gm.) occurred in the postthyroid period (Period 3).

The calcium oxid elimination in the feces during twenty-five days varied in the forethyroid period (Period 1) from 97.8 to 73.7 (Period 3) and was 76.6 per cent. at the close of the experiment. Secchi, working on normal persons, found from 40 to 60 per cent. of the calcium eliminated in the feces. Thus in this patient there was appar-

68. Secchi: Biochem. Ztschr., 1914, lxxvi, 156.

ently a deficient elimination and poor absorption of calcium from the intestine. An improvement in absorption of 16.6 per cent. occurred during thyroid administration, which increased in the postthyroid period (Period 3) to 24.1 per cent. The metabolism continued at a slightly lower level (2.9 to 3.8 per cent.) during the thymus and postthymus periods. That is, calcium metabolism remained practically the same in the last two periods. Bergeim, Stewart and Hawk[69] in studying the metabolism of a case after thyroparathyroidectomy, also found low calcium in the urine (1/121 of that in the feces). McCrudden and Fales[70] found in a normal boy a retention of 17.1 per cent. calcium oxid per day of 2.5 gm. ingested, while one fifth of the excreted calcium occurred by way of the urine. Sherman, Mettler and Sinclair[71] in their experiments report that calcium in the urine varied from 3.9 per cent. to 23.7 per cent. Determann[72] states that phos-

TABLE 21.—METABOLISM OF CALCIUM (CALCIUM OXID) IN ALL PERIODS (RELATIVE AND ABSOLUTE) *

	Calcium Oxid, Gm.					Calcium Oxid, per Cent.				
	1	2	3	4	5	1	2	3	4	5
Ingestion	1.032	1.062	1.021	1.002	1.019	.....	.....	.....	.....	.....
In feces	1.007	0.861	0.754	0.776	0.782	97.8	81.2	73.7	77.5	76.6
In urine	0.016	0.019	0.018	0.013	0.018	1.54	1.81	1.79	1.24	1.78
Retention	0.01	0.182	0.248	0.216	0.219	0.94	17.1	24.33	21.5	21.47

* Maximum retention 23.39 per cent. (Period 3).

phorus and calcium excretion into the intestine is increased in exophthalmic goiter during thyroid treatment. Results obtained on the patient discussed above do not bear this out and do not confirm the results obtained by Falta, Tedesco and Bolaffio,[45] who found on thyroidectomized dogs no diminution in the metabolism of the mineral salts in the first days of hunger. There appeared, however, they report, to be a decreased excretion of sodium chlorid, also calcium, phosphorus and magnesium in the urine while on the administration of thyroid gland there was a rise in the calcium and phosphorus in the feces and of magnesium in the urine.

Further work[68] indicated that while in young children there is a retention of calcium in the normal adult there is a tendency for a calcium balance or equilibrium on varied diets containing from 0.4 to

69. Bergeim, Stewart, and Hawk: Jour. Exper. Med., 1914, xx, 225.
70. McCrudden and Fales: THE ARCHIVES INT. MED., 1912, ix, 287.
71. Sherman, Mettler and Sinclair: U. S. Dept. Agr. Bull. No. 227, 1910, O. E. S., p. 38.
72. Determann: Verdauung u. Stoffwechsel-Krankheiten, 1914, v, 60.

1.5 gm. calcium. Schabad,[73] among numerous calcium balance experiments in rickets, found an increased calcium excretion through the feces in the progressive stage of the disease; the calcium excretion through the urine was subnormal, but during convalescence above normal.

SULPHUR METABOLISM

The periods immediately following thyroid and thymus feeding, Periods 3 and 5, respectively, showed an increase within narrow limits in sulphur elimination through the feces (5.1 per cent., 0.048 gm., and 1.4 per cent., 0.045 gm.).

TABLE 22.—METABOLISM OF SULPHUR IN ALL PERIODS (RELATIVE AND ABSOLUTE) *

	Sulphur, Gm.					Sulphur, per Cent.				
	1	2	3	4	5	1	2	3	4	5
Ingestion	0.892	0.892	0.892	0.892	0.892	.....	.....	.....	.....	.....
In feces	0.117	0.119	0.164	0.149	0.162	13.08	13.3	18.4	16.7	18.1
In urine	0.752	0.652	0.629	0.619	0.52	84.4	73	70.5	69.4	58.4
Retention	0.023	0.121	0.099	0.124	0.21	2.57	13.56	11.06	13.85	23.56

* Maximum retention 20.99 per cent. (Period 5).

The excretion of sulphur by way of the urine underwent a diminution during the posttreatment periods (Periods 3 and 5) of 2.5 per cent. and 11.0 per cent. Thyroid and thymus administration had slight effect on the excretion of sulphur in the feces, except that in the postthyroid period (Period 3) sulphur excretion went up slightly, though less than 5 per cent., and remained near this level. In the urine there was a gradually decreasing excretion of sulphur from 84.4 per cent. (Period 1) to 58.4 per cent. (Period 5), a difference of 26 per cent. (0.232 gm. sulphur). The sulphur metabolism shows certain peculiarities. In the first place, in Period 1 there is no loss of sulphur such as occurred for phosphorus and nitrogen. The retention during the thyroid and thymus periods is approximately the same. There was only 26 mg. more sulphur metabolized during the thymus feeding. Decreased absorption occurred during the postthyroid period (Period 3), while in the postthymus period (Period 5) there was a considerable increase in metabolism, retention going from 0.124 gm. to 0.210 gm., or from 13.85 per cent. to 23.56 per cent. In the urine there was a gradual decrease from 0.752 to 0.520 gm., or a difference of 0.232 gm. from Period 1 to Period 5, amounting to 26 per cent. The administration of thyroid and thymus caused no rise of sulphur in the urine,

73. Schabad: Arch. f. Kinderheilk., 1910, liii, 380.

as occurred in feces. The retention was considerable in both treatment periods, 0.121 gm. in Period 2 and 0.124 gm. in Period 4, respectively, but greatest in Period 5, a total of 0.210 gm. (23.56 per cent.). Thus the sulphur excretion offers no suggestion of tissue disintegration.

Urinary Indican: The daily output of indican in the urine was determined by Jolle's colorimetric method. The average daily excretion of indican for each of the periods of study was as follows:

Period	Indican, Mg.
Foreperiod	25.2
Thyroid	12.6
Postthyroid	9.0
Thymus	10.0
Postthymus	4.4

It will be noticed that following thyroid treatment and coincident with improvement in nitrogen balance and in the condition of the patient there was a progressive decrease of urinary indican excretion. This may indicate decreased putrefaction, as it is associated with improved absorption of the food elements. The slight increase on thymus administration confirms certain work by Moraczewski, who found that the ingestion of thymus and certain other glandular tissues led to an increase in indican excretion.

SUMMARY AND CONCLUSIONS

A study was made of the metabolism of nitrogen, phosphorus, sulphur, calcium and magnesium on a patient with exophthalmic goiter, with apparently a slight hypothyroidism, and responding readily to treatment. The study was made in five periods of five days each, including periods of thyroid and thymus treatment.

In the preliminary period without treatment a marked disturbance of metabolism was noted, with pronounced losses of nitrogen, phosphorus, and magnesium and a practical balance of calcium and sulphur. The loss of nitrogen by the feces was much greater than that of an average normal person.

Thyroid treatment markedly stimulated the metabolism of all elements determined, this stimulation continuing long after treatment was stopped. Considerable retention of all elements was brought about, the maximum effect being reached sooner in the case of calcium and magnesium than in the case of nitrogen, sulphur and phosphorus. The retentions of the former reached their maximum in the third (postthyroid) period, while the latter showed a progressive increase in retention to the end of the experiment.

Slightly better intestinal absorption of nitrogen followed treatment, although the loss of nitrogen by the feces continued high. The intestinal absorption of other elements, with the exception of calcium,

varied but slightly. The urinary excretions of all elements except calcium markedly decreased after thyroid treatment, corresponding with the retention of these elements.

A retention of calcium was brought about, this reaching a maximum of 24.33 per cent. in the postthyroid period. The urinary calcium excretion was extremely low (2 per cent. of the intake) and continued so. The excretion of this element by the feces was markedly diminished, indicating better intestinal absorption.

The effect of thymus administration on the metabolism was less marked than that of the thyroid, but appeared to be distinct. In the thymus period the retention of all elements was depressed. When thymus administration ceased, the rate of retention for all elements immediately increased. Thus thymus treatment appeared to depress the stimulating effect of the thyroid on metabolism, which supports the view of a possible antagonistic action of these glands, such as has been suggested by others on the basis of indirect evidence.

The administration of thyroid caused diuresis immediately. Thymus treatment had the opposite effect, leading to a retention of water, with marked decrease in urine volumes (from 2,472 to 1,239 c.c.) on constant water ingestion.

The weight of the patient decreased on thyroid treatment and increased after withdrawal and on thymus administration. The variations (from 6 to 8 pounds) were apparently due in part to loss or gain of nitrogenous tissue constituents, but in the main to loss of water on thyroid treatment and retention on its discontinuance or on thymus treatment.

Following thyroid treatment there was a progressive decrease in urinary indican excretion. This may indicate lessened intestinal putrefaction.

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THE RELATION OF CHANGES IN THE FORM OF THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM TO FUNCTIONAL CHANGES IN THE HEART *

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Constancy of form is one of the most striking characteristics of electrocardiograms obtained at various times from the same individual. Any change in form is therefore of interest, as it indicates some alteration in the passage of the impulse of contraction through the heart or some change in the manner of the muscular contraction. Changes in heart rate and in the force of contraction are not, as a rule, accompanied by definite alterations in the form of the electrocardiogram.

The ventricular portion of the electrocardiogram is composed of a series of waves and is initiated by a group of three waves, the so-called Q, R, S group. Of these, only the R wave is constant in normal individuals in records obtained by the three leads of Einthoven. There are at present differences of opinion as to the functional activity of the ventricles responsible for this group of waves. Without taking up the various points in this controversy, it may be said that the evidence is in favor of the hypothesis that it is the passage of the impulse through the ventricles rather than the actual muscular contraction which gives rise to this part of the electrocardiogram and initiates the ventricular complex. As Einthoven[1] has suggested this Q, R, S group deserves a closer examination than has been hitherto given to it in clinical electrocardiography, as it shows the path by which the excitation wave is conducted from the auricles to all parts of the ventricular walls. It is to changes in this initial part of the ventricular electrocardiogram that attention is directed in this paper.

Before discussing the type of change to be described, it is necessary to consider several well-defined abnormalities of the ventricular complex which are frequently encountered in clinical electrocardiograms, and which are well understood, because they have been repeatedly reproduced under experimental conditions. The commonest of these is that caused by the passage of impulses arising in some abnormal point in the ventricles, the so-called ectopic stimuli, which give rise

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1. Einthoven: Different Forms of the Human Electrocardiogram and Their Significance, Lancet, London, 1912, i, 853.

to ventricular premature contractions or extrasystoles. When this occurs the impulse passes through the ventricles in abnormal directions, yielding a ventricular complex which is, as a rule, much deformed.

Another well-defined abnormality of the ventricular complex is caused when an impulse which reaches the ventricles by the usual path is hindered in its passage throughout the ventricles by a derangement of one of the branches of the conducting system which should convey the impulse either to the right or to the left ventricle. Such a condition of bundle-branch block has been produced in animals by cutting one or the other of the main branches of the conducting system. This procedure is followed by a great change in the form of the electrocardiogram, as first described by Eppinger and Rothberger.[2] Electrocardiograms similar to those obtained after this experimental procedure have been obtained from patients whose hearts have later shown, on histologic examination, a lesion of one or the other of the main branches of the conducting system. A sufficient number of cases have been studied to justify the diagnosis of the lesion from the type of the electrocardiogram. Carter,[3] who reported twenty-two cases of bundle-branch block, has pointed out the requirements of the form necessary to establish the diagnosis. The initial Q, R, S group of the ventricular complex exceeds the normal time 0.1 second; the waves are large, of bizarre forms, and the final deflection T is directed oppositely to the initial ventricular wave.

Changes in the distribution of muscle mass between the two ventricles, as occurs in cardiac hypertrophy, also leads to alterations in the form of the electrocardiograms, which is especially noticeable when the records obtained by the three usual leads are compared with one another. These changes have been recently demonstrated experimentally by Fraser.[4] They are especially noteworthy in cases of congenital malformation of the heart. That the marked changes in the form of the electrocardiogram which occur in this condition are dependent on the abnormal distribution of the muscle mass between the two ventricles has been clearly demonstrated recently in our laboratory by McCulloch.[5] One other change in the form of the electrocardiogram remains to be mentioned, which is frequently encountered clinically, namely, alterations in the size or direction of the final wave of the complex, the so-called T wave. This wave, which is normally a long, well-defined upwardly directed wave, may become diminished

2. Eppinger and Rothberger: Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, Ztschr. f. klin. Med., 1910, lxx, 1.

3. Carter: Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle, THE ARCHIVES INT. MED., 1914, xiii, 803.

4. Fraser: Changes in the Electrocardiograms Accompanying Experimental Changes in the Rabbit's Heart, Jour. Exper. Med., 1915, xxii, 292.

5. McCulloch: Am. Jour. Dis. Child., 1916, xii, 30.

in size, disappear or become inverted. Such a change is frequently observed in heart disease, especially when the myocardium is damaged. Kraus and Nicolai[6] have laid stress on the inverted or negative T wave as an indication of myocardial weakness, and probably all who have made use of the electrocardiogram in the study of clinical material will agree that this change frequently accompanies other signs of myocardial disease. The fact, however, that such a change takes place in the T wave when digitalis is administered, as pointed out by Cohn, Fraser and Jamieson,[7] renders its significance uncertain as an indication of myocardial weakness. It is mentioned here as being the one change in form of the ventricular complex which has been hitherto recognized as giving evidence as to the functional efficiency of the heart muscle.

The object of the present paper is to discuss a series of records which show changes in the form of the ventricular electrocardiogram differing from those that have been mentioned. These changes consist in alterations in the form of the Q, R, S group which are apparently dependent on a functional derangement of the ventricles, hindering the normal spread of the impulse of contraction. The spread of the impulse is hindered in some cases because the conducting system of the ventricles has not had a sufficient time to recover from the effects of an impulse that has just caused a ventricular contraction, while in other cases the recovery of the intraventricular conduction is abnormally delayed, so that the impulse spreads through the ventricles properly only after a prolonged period of ventricular rest. In some instances in which a prolonged rest does not occur the electrocardiogram is of a form which indicates that the proper spread of the impulse through the ventricles is constantly lacking. Changes in form of the complexes have been observed to occur from time to time parallel to the clinical course of cardiac cases. A consideration of these changes indicates that the electrocardiographic method may demonstrate functional deficiency of the conducting system in the ventricles and in this way be a means of revealing diminished functional capacity of the ventricles.

The records have been obtained by means of the Edelmann type of string galvanometer. In all instances the tension of the string has been so adjusted that the passage of two millivolts through it, with the patient in the circuit, results in a deflection on the record of two centimeters. Only those records have been used in which this adjustment did not render the string sufficiently slack to cause any marked fling,

6. Kraus and Nicolai: Das Elektrocardiogram, Leipzig, 1910, p. 278.

7. Cohn, Fraser and Jamieson: The Influence of Digitalis on the T Wave of the Human Electrocardiogram, Jour. Exper. Med., 1915, xxi, 593.

which results in a definite deformity of the curves. Omitting this precaution leads to striking errors. In lettering the curves the single letter R is used to mark the Q, R, S group.

CASE 1.—J. B., a man, 42 years of age, had been aware of an irregularity of the pulse since boyhood. Except for a heightened blood pressure (systolic 148 mm. of mercury, diastolic 95), moderate cardiac enlargement and a trace of albumin in the urine, he gave no signs of disease. He had never had a serious acute illness, and his only excess had been very constant hard work as a lawyer. His life had always been one of unrestricted activity. An examination was undertaken only as a means of determining the type of cardiac arrhythmia. Electrocardiograms (Fig. 1) revealed a sino-auricular block, a complete cardiac cycle being omitted every few beats. The arrhythmia was complicated, however, by the occurrence of an idioventricular beat, always occurring near the end of the long pause caused by the missed beat and immediately before the auricular contraction which initiated the restoration of the regular rhythm. This idioventricular beat yielded a complex practically identical with that of the normal beats, indicating that it arose in the junctional tissues before the division of the conducting system, and that the impulse spread through the ventricles in a normal manner.

The special interest in this record centers on the complexes yielded by the ventricular responses to the auricular contractions which occur immediately after the onset of the idioventricular contractions. The records furnish twenty-five examples of this combination. The electrocardiograms show that the ventricular responses to these auricular contractions vary with the time that elapses between the onset of the idioventricular beats and the auricular contractions. When this time is less than 0.15 of a second, usually no ventricular response follows the auricular contraction. As this time lengthens the ventricles respond, but when it is only a little longer than 0.15 of a second, the response is abnormal, as indicated by a prolonged auriculoventricular conduction time and by a markedly deformed ventricular complex.

The longer the time between the onset of the idioventricular contraction and the following auricular contraction, the shorter becomes the auriculoventricular conduction time and the nearer to the normal becomes the form of the ventricular complex. The more abnormal ventricular complexes show a prolongation of the time occupied by the Q, R, S group, which distinctly exceeds the normal time of 0.1 of a second. Both the ascent and descent of the R wave is more gradual than normally and there is a blunt, notched, or broken apex to the R wave, which is often distinctly diminished in height. The complexes are those to which Lewis[8] has applied the term "aberrant."

These changes in the ventricular complexes of the electrocardiogram are interpreted as follows: At times the impulse from the auricular contraction reaches the ventricles when they are still in

8. Lewis: Observations on Disorders of the Heart's Action, Heart, 1912, iii, 279.

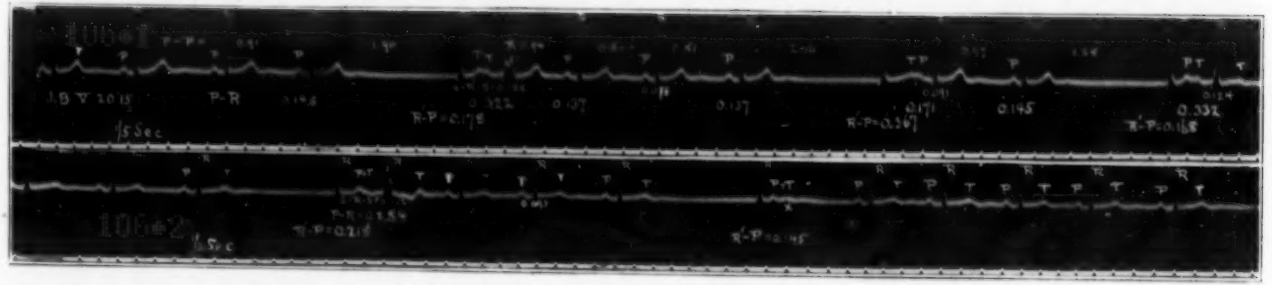

Fig. 1 (Case 1).—Sino-auricular block, with idioventricular contractions. The abnormal ventricular complexes are yielded by contractions which occur before the ventricles have recovered from a previous contraction.

the refractory phase, and so no ventricular response results. Usually the impulse reaches the ventricles when they have only partly recovered, and the conduction through the ventricles is depressed under these conditions, the impulse is delayed in part of the usual course, or follows an abnormal course, being blocked along some of its usual paths. Thus the intraventricular conduction apparently shows the same depression as is present in the auriculoventricular conducting system. The prolonged auriculoventricular conduction time is in part responsible for the degree of recovery which takes place in the ventricles, as this adds to the time between the idioventricular contraction and the ventricular contraction which follows.

The electrocardiograms of this case illustrate the changes in the form of the ventricular complex which are caused by functional derangement of the ventricles, when a contraction occurs before the ventricles have fully recovered from a previous contraction. They indicate also that the degree of abnormality of the complex parallels the degree of depression of the intraventricular conduction.

CASE 2.—S. B., a woman of 63 years, suffered from atrophic cirrhosis of the liver, chronic myocarditis and chronic valvular cardiac disease (mitral insufficiency). On May 2, 1915, when the first record was made, she was cyanotic, markedly dyspneic, and there was general anasarca. The heart was much enlarged, cardiac dulness extending 18.5 cm. to the left of the midsternal line, and besides the systolic murmur in the apex region there was a pericardial friction rub. The heart was beating at a rate of 87 per minute, and the systolic blood pressure was 110 mm. of mercury, the diastolic 65 mm.

The electrocardiograms (Fig. 2) are very abnormal in form. The Q, R, S group is composed of a series of waves, none of which resemble those of the normal electrocardiogram. The period of time occupied by the occurrence of this group of waves is distinctly longer than the normal 0.1 of a second.

On May 18, when electrocardiograms were again obtained (Fig. 3), the patient was much improved. The dyspnea, cyanosis and edema were distinctly less. The systolic blood pressure had risen from 110 to 120 mm. of mercury without change in the diastolic pressure. The heart rate was 82 per minute. The electrocardiograms show an arrhythmia caused by premature contractions of auricular, nodal and ventricular origin. There is a distinct change in the form of all ventricular complexes as compared with those seen in Figure 2. The most striking feature of the record is the change in the form of the ventricular complexes which occur after a period of increased ventricular rest. This change is seen after the compensatory pause following premature ventricular beats and when premature auricular beats are blocked. Under these conditions the ventricular complexes are much more nearly normal in form.

This case illustrates that changes in the form of the ventricular complexes may occur with improvement of the cardiac efficiency, as evidenced by the clinical improvement, and with increased periods of ventricular rest. The usual diastolic pause between the regular beats was not long enough to allow the intraventricular conduction to recover sufficiently to allow the impulse to pass normally. This case is, therefore, an example of those in which the recovery of the intra-

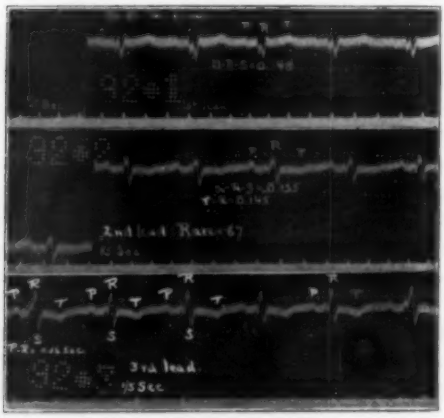

Fig. 2 (Case 2).—First record, May 2, 1915. Form of ventricular complexes abnormal in all leads. The Q, R, S time is prolonged; P-R time normal. The patient showed signs of marked cardiac decompensation.

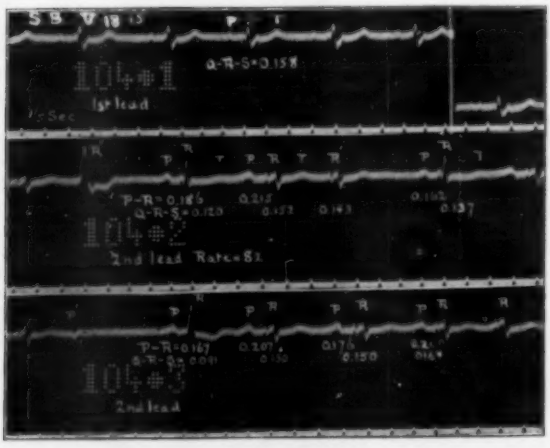

Fig. 3 (Case 2).—Second record, May 18, 1915. The form of ventricular complexes differs from that seen in Figure 2. The Q, R, S time and the P-R time are distinctly prolonged; the form of the ventricular complexes more nearly normal after a prolonged ventricular rest. The patient showed distinct clinical improvement.

ventricular conduction is abnormally delayed, so that the impulse spreads through the ventricles properly only after a prolonged period of ventricular rest.

CASE 3.—A man, 33 years of age, came into the outpatient department complaining of pain in the chest and shortness of breath. The heart dulness extended 5 cm. to the right and 15 cm. to the left of the midsternal line. The heart sounds were distant and blurred, and the heart was beating very rapidly and irregularly. The electrocardiograms (Fig. 4) obtained on this day show a heart rate of 174 per minute. The ventricular complexes occur irregularly and are of unusual forms, while no auricular complexes are visible. The main ascents and descents of the Q, R, S group are gradual, and the time occupied by this group is distinctly prolonged, but difficult to determine accurately. The slight variation of form from beat to beat may be caused by combinations of ventricular complexes with the waves of auricular fibrillation. The patient refused to remain in the hospital. He was put on digitalis and returned in forty-eight hours, after two drams of the tincture had been taken. On this admission there was distinct improvement in symptoms and the heart rate was greatly reduced, varying from 77 to 100 beats per minute. Electrocardiograms (Fig. 5) obtained this day are typical of auricular fibrillation. The arrhythmia is much more marked, and after the longer diastolic pauses, the ventricular complexes have a much more normal form than after the shorter pauses. This is especially noticeable in the first lead, where the abnormal, blunt, low complexes, composed of an R wave with a slow ascent and descent become, after prolonged diastoles, sharp pointed, higher waves resembling closely those usually seen in auricular fibrillation. A study of the various records convinces that this change in form is not caused by combinations of the ventricular complexes with the waves of auricular activity. The fact that this patient died suddenly two days after his second visit, when under a severe emotional strain, suggests that the heart muscle was badly damaged.

The case is one in which the ventricles responded to impulses from the fibrillating auricles at a very rapid rate, and the periods between contractions were not of sufficient duration to allow complete recovery of the intraventricular conduction. The cardiac slowing which resulted from the administration of digitalis caused some improvement in this respect, and resulted in longer ventricular rests, which were followed by ventricular contractions yielding normal or nearly normal complexes.

CASE 4.—A man, aged 59, suffering from syphilis and complete heart block, was under almost continuous observation for a period of nearly two years, during which time numerous electrocardiograms were obtained. During the first six months he had many attacks of unconsciousness and convulsions, with prolonged periods of ventricular inactivity, giving the typical picture of Stokes-Adams syndrome. After March, 1914, these did not occur, and electrocardiograms similar to those shown in Figure 6 were constantly obtained until June 26, 1915. On this day a marked change in the form of the ventricular complexes was noted (Fig. 7). It is seen that a marked change occurs in the form of the Q, R, S group in all leads and the time occupied by the group greatly exceeds the normal. The broad form with the notched top seen in the first lead is especially noteworthy, as it resembles closely the abnormal form seen in the first lead of the first and third cases.

On the day before the record was made the patient had three short "sinking spells," in which he became semiconscious. These spells lasted two

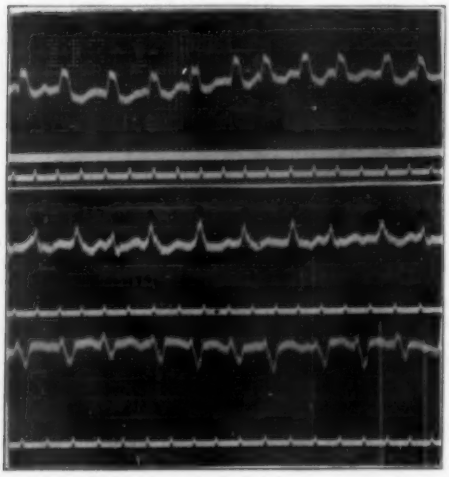

Fig. 4 (Case 3).—May 24, 1915. Auricular fibrillation; very rapid ventricular rate, with markedly deformed ventricular complexes.

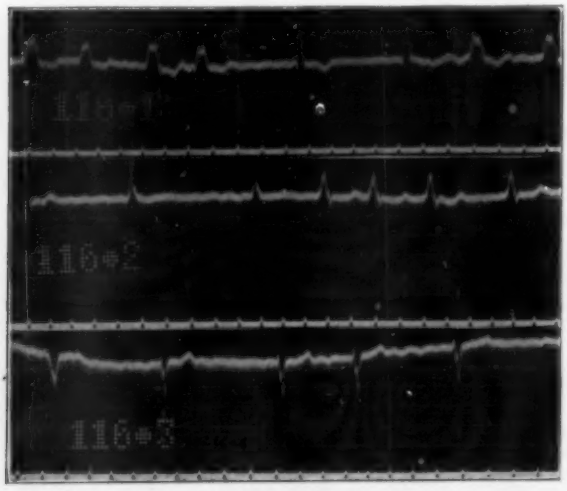

Fig. 5 (Case 3).—May 26, 1915. Auricular fibrillation; after taking tincture of digitalis for forty-eight hours. Striking change in the form of the ventricular complex after ventricular pauses, especially in the first lead.

or three minutes only and came on just as the patient was about to "drop off" to sleep. These spells continued for several days and gradually disappeared. There was no change in the pulse rate at these times of syncope, it remaining between 35 and 43 per minute. During the time when these attacks of syncope occurred the patient was in a critical condition. There was marked cyanosis, dyspnea, Cheyne-Stokes respiration and collections of fluid in the chest, peritoneum and lower extremities. His death was expected hourly, and there seemed to be extreme cardiac insufficiency. But he gradually improved, however, and July 5 he was much better, the cyanosis, dyspnea and edema being less marked. On this date electrocardiograms (Fig. 8) showed another change in form. The following note was made just after the records were taken: "Electrocardiograms taken this afternoon show a very interesting alternation in the form of the Q, R, S group of the ventricular complexes. They are first of the type formerly seen and then of the type which appeared constantly a week or so ago. There is apparently no difference in the effectiveness of the ventricular contractions yielding the varying complexes, as no alternation of the pulse is noted in an examination made directly after the records were obtained, either by palpation of the radial pulse or by auscultation over the brachial artery with the sphygmomanometer applied. The systolic blood pressure is 105 mm. of mercury, the diastolic 45. All beats come through with equal intensity."

At first sight one would be inclined to interpret these changes in form as being caused by contractions set up by impulses arising from two distinct foci, resulting in the passage of the impulses along two different sets of paths. A record obtained with the first lead, however, is evidence for the belief that the impulse of contraction was spreading properly through the ventricles only in alternate beats (Fig. 9). It is seen in this record that a transition form occurs (the third and fifth complexes), suggesting that the spread of the impulse was either not always complete or was not at the same rate through each ventricle. This conception of the variations in the spread of the impulse seems to explain these transition forms of ventricular complexes more satisfactorily than assuming the presence of a shifting focus of stimulus formation.

By July 27, 1915, the patient's condition was greatly improved. He no longer had dizzy spells and was able to be up and about. The electrocardiograms on this date were of the same form as seen previous to the period of marked cardiac insufficiency (Fig. 10).

This case shows a transient but extremely marked change in the form of the ventricular complexes during complete heart block, occurring during a period of great cardiac insufficiency. The abnormally slow rate of the ventricles allows the element of functional fatigue alone to be ruled out. Here the intraventricular conduction was so deranged that the long ventricular pauses at first did not lead to its recovery, while later the intraventricular conduction was apparently normal or partially recovered in alternating beats. Finally the form of the complexes returned to what must be considered the normal for this case, showing that the functional derangement of the ventricles responsible for the change in form was transient.

CASE 5.—A colored woman, aged 30, suffered from a generalized infection with *Streptococcus viridans*, acute endocarditis, embolism, cardiac dilatation and hypertrophy and syphilis. On Oct. 17, 1915, she had moderate dyspnea. The cardiac dulness extended 3.5 cm. to the right and 12 cm. to the left of the midsternal line. The heart rate was 91 per minute, while the systolic blood pressure was 120 mm. of mercury, the diastolic 72. There were no marked

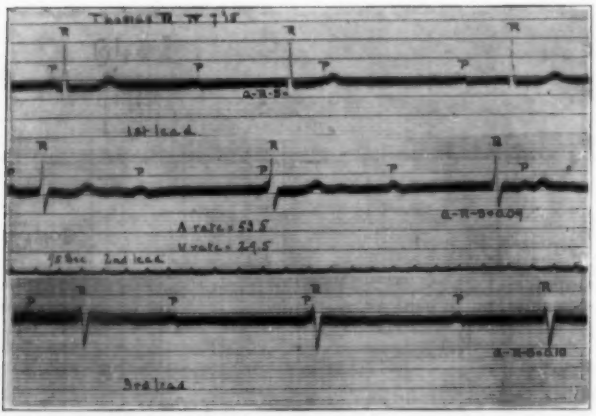

Fig. 6 (Case 4).—April 7, 1915. Complete heart block; the usual type of ventricular complex; normal Q, R, S time.

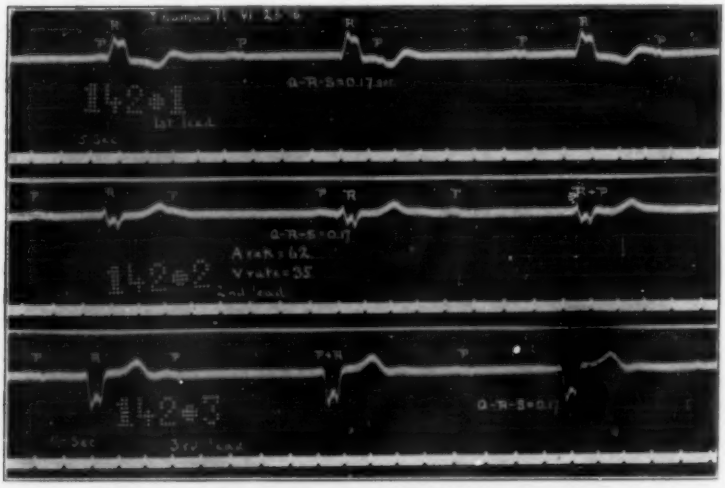

Fig. 7 (Case 4).—June 26, 1915. Striking change in form of the ventricular complex accompanying severe symptoms. Compare with Figure 6.

signs of cardiac insufficiency. The electrocardiograms obtained on this day showed high R waves, with sharp ascents and descents in all leads (Fig. 11).

On Dec. 11, 1915, the patient was very ill and showed definite signs of decompensation. The systolic blood pressure had fallen 27 mm. of mercury, while the diastolic pressure was unchanged. The heart rate was 110. The outline of cardiac dulness was unchanged. Electrocardiograms (Fig. 12) show a distinct change in form of the ventricular complexes, the R waves being much less high, and the ascent and descent, especially in the first lead, being slow. The Q, R, S time is not, however, definitely changed.

In this case well-defined changes in the ventricular complexes occurred synchronously with distinct decrease in cardiac efficiency. The form of the complexes resembles sufficiently those accompanying definite functional depression in the previous cases to suggest that the change which occurred during failure of the cardiac efficiency is the result of the cardiac failure and indicates presumably derangement of the intraventricular conduction.

CASE 6 is an example of change in form of the ventricular complex which occurred synchronously with a marked improvement in symptoms and apparently because of functional improvement of the ventricles. The patient was a woman of 24 who suffered from aortic and mitral insufficiency and who showed at times alternation of the heart beat. On June 17, 1915, when the record shown in Figure 13 was obtained, there was dyspnea while at rest in bed and other signs of cardiac decompensation. The electrocardiogram shows a slightly slowed ascent and descent in the R waves, and in Lead I the blunt, split-topped form is seen, which suggests that seen in some of the previous cases.

These abnormalities are less marked, and almost absent in records obtained on May 24, 1916 (Fig. 14), when the patient was no longer in the hospital, but returned merely for observation. On this day there was slight dyspnea after walking to the heart station, but no other symptoms suggesting cardiac insufficiency.

The change in form in the ventricular complexes which accompanied marked improvement of the cardiac efficiency seems to indicate that the abnormalities of the complexes observed during definite decompensation were dependent on the cardiac insufficiency. The fact that in this case alternation of the heart beat was not accompanied by alternation in the form of the ventricular complexes is evidence in favor of the belief that the abnormalities seen in Figure 13 were not caused by changes in muscular contractions as such, and makes it appear more likely that they resulted from defective conduction of the impulses through the ventricular musculature.

CASE 7 is included as one of marked cardiac decompensation, which showed abnormal ventricular complexes similar to those seen in the previous case. The electrocardiogram (Fig. 15) was obtained from a man with aortic insufficiency of syphilitic origin, whose heart was evidently much dilated. Here again the gradual ascent and descent of the limbs of the R waves are seen, especially in the second lead. The same blunt, notched wave is seen in the first lead, while the third lead complex is distinctly peculiar. The patient died suddenly a few days after the record was obtained, following the intravenous administration of strophanthin. It seemed not unlikely that ventricular fibrillation resulted from the administration of the drug.

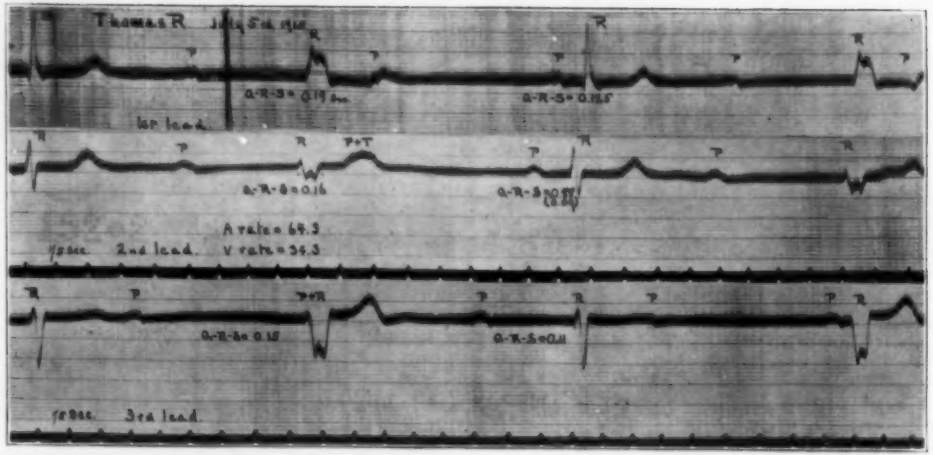

Fig. 8 (Case 4).—July 5, 1915. The form of the complexes alternate; first the usual form and then the form that appeared nine days previously.

Fig. 9 (Case 4).—July 5, 1915. Transition between the old and the new forms of the first lead complexes.

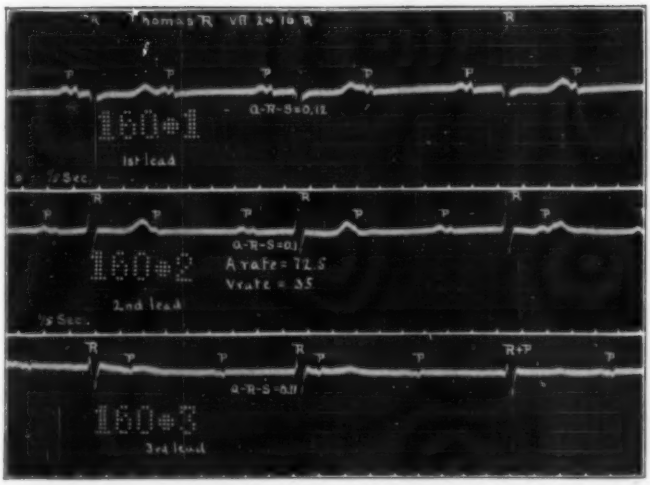

Fig. 10 (Case 4).—July 24, 1915. The form of the ventricular complexes is constantly that seen before the marked change occurred. No further change occurred.

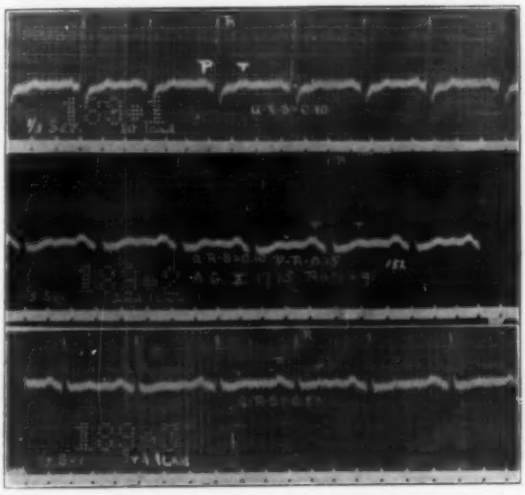

Fig. 11 (Case 5).—Oct. 17, 1915. Cardiac efficiency but slightly impaired.

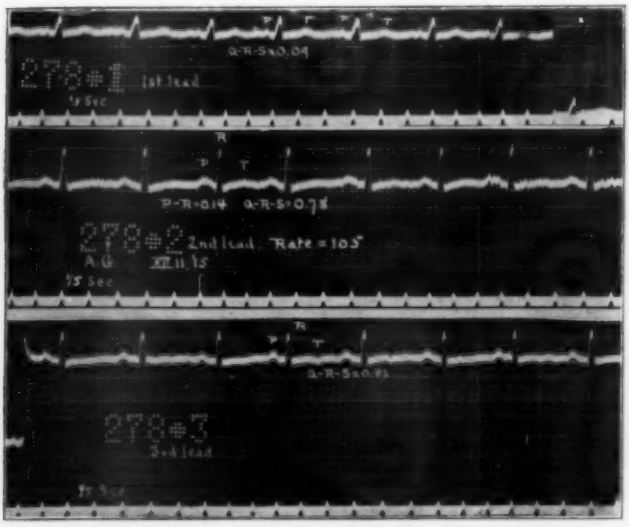

Fig. 12 (Case 5).—Dec. 11, 1915. Cardiac efficiency much impaired.

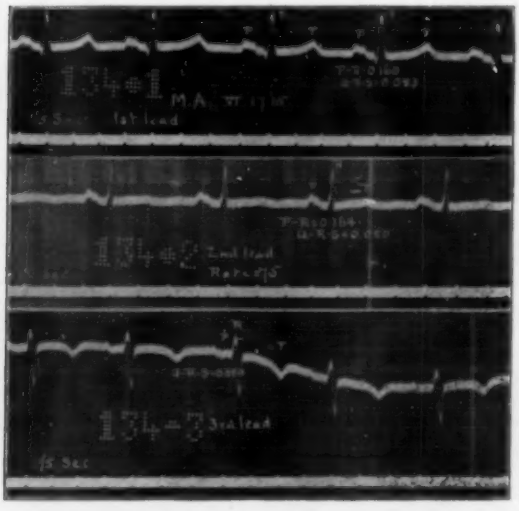

Fig. 13 (Case 6).—June 17, 1915. Marked signs of cardiac decompensation.

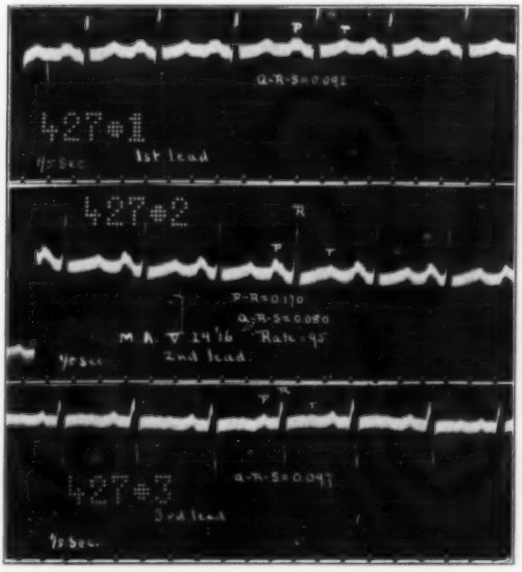

Fig. 14 (Case 6).—May 24, 1916. Patient much improved; cardiac decompensation slight.

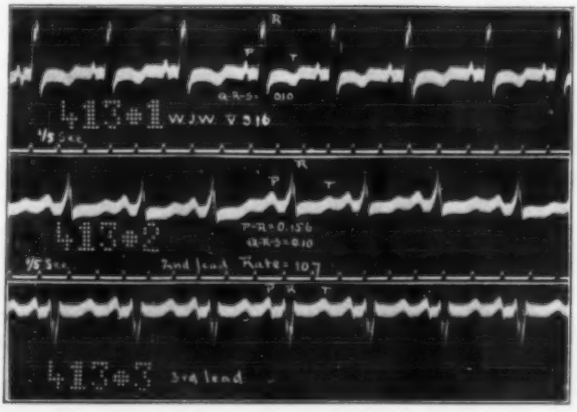

Fig. 15 (Case 7).—May 3, 1916. Patient showed signs of extreme cardiac decompensation.

COMMENT

The idea that changes in form of the ventricular complexes may depend on faulty conduction through the ventricles of impulses descending from the auricles was first suggested by Lewis.[9] He based his hypothesis on records obtained under experimental conditions, as well as on electrocardiograms from clinical material, and developed his idea further in a second paper.[8] He points out the association of prolonged auriculoventricular conduction with the so-called aberrant contractions, and suggests that abnormal complexes may depend on damage affecting special branches of the intraventricular conducting system. Under such conditions the impulse is at one time transmitted through the whole arborization, while at other times it passes into the arborization, but fails to course along certain given channels.

Hart[10] has also recognized derangement of intraventricular conduction as a cause of contractions yielding abnormal ventricular complexes. He shows records in which the Q, R, S group of the complex is deformed in a manner somewhat similar to deformities described in this paper and he believes that the abnormalities are caused by damage to the musculature, so that the passage of impulses is interfered with in all parts of the conducting system.

The occurrence of varying ventricular complexes in cases of complete heart block has been reported by Cohn[11] and by Oppenheimer and Williams.[12] These cases have been interpreted as examples of either a shifting focus of stimulus formation within the ventricles or as interference with intraventricular conduction. The changes in form of the ventricular complexes of the case reported here are considered as dependent on interference of ventricular conduction.

The purpose of this paper is not primarily to record a series of cases showing derangement of intraventricular conduction. This change in function is discussed only as affording an explanation of the changes in form of the ventricular complexes which have been observed. The object of the paper is to point out certain abnormalities occurring in electrocardiographic curves which apparently accompany functional deficiency of the ventricles. This is done with the hope that the electrocardiographic method may sometimes prove of value in determining

9. Lewis: Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Auricular Musculature, Heart, 1910, ii, 23.

10. Hart: Paroxysmal Tachycardia, Heart, 1912, iv, 128.

11. Cohn: A Case of Transient Complete Auriculoventricular Dissociation, Showing Constantly Varying Ventricular Complexes, Heart, 1913, v, 5.

12. Oppenheimer and Williams: Prolonged Complete Heart Block, Without Lesion of the Bundle of His and with Frequent Changes in the Idioventricular Electrical Complexes, Proc. Soc. Exper. Biol. and Med., 1913, x, 86.

changes in the functional capacity of the ventricular musculature, perhaps the most important and one of the most obscure problems involved in the study of the heart.

Only a much wider experience and a collection of many such cases as those exemplified in this paper can determine the value of these observations from the purely clinical point of view.

SUMMARY

A series of cases is reported which yielded electrocardiograms showing abnormal ventricular complexes. These abnormalities consist in changes in the initial portion of the complexes, the Q, R, S group, and differ from those yielded by contractions caused by ectopic stimuli and from those changes which occur with bundle-branch block.

These abnormalities are apparently dependent on derangement of the intraventricular conduction, which prevents the passage of the excitation wave either along the usual paths or at the usual rate throughout the ventricles.

The normal spread of the impulse is hindered because the impulse reaches the ventricles before the conducting system has recovered from the preceding contraction, and the records indicate in some cases that this derangement disappears with prolonged ventricular rest.

These observations are taken as evidence for the belief that in cases in which the ventricular complexes constantly show certain abnormal forms, there are functional changes in the heart which prevent the normal recovery of intraventricular conduction during diastole. It is shown that changes in form of the ventricular portions of the electrocardiogram may occur synchronously with functional changes in the heart, and evidence is offered for the belief that certain abnormalities in the form of the electrocardiogram indicate functional derangement of the ventricles.

A STUDY OF LOW BLOOD PRESSURES NOT ASSOCIATED WITH TRAUMA OR HEMORRHAGE *

J. P. SIMONDS, M.D.
CHICAGO

In the course of studies on anaphylactic shock in the dog it was found that during the period of low blood pressure the pressor effect of nicotin may be greatly augmented at a time when epinephrin produces little or no result.[1] Exactly similar reactions were found in peptone shock. Low blood pressures from hemorrhage are sharply distinguished from the above by the fact that in them, while the effect of nicotin may be exaggerated, that of epinephrin remains unchanged, as shown by Hoskins, Rowley and Rosser.[2] It seems not improbable, therefore, that the mechanism of these phenomena may be different.

It was suggested in connection with the study of anaphylactic shock that the augmented action of nicotin in that condition was due largely if not entirely to its effect on respiration. Further observations on this point are here reported, partly because they may have some bearing on the question of the effect of respiration on blood pressure, and partly because they may find practical application in the treatment of certain forms of shock.

The technic employed was that used in the previous study, namely, that described by Hoskins and Wheelon.[3] The animals were anesthetized with ether. A canula in the carotid or femoral artery was connected with a mercury manometer. A second canula in the femoral vein was connected with a buret containing physiologic salt solution, with a pinch-cock on the rubber connection immediately above the canula. Standard doses of nicotin (1 c.c. of 1 to 4,000 solution) and of epinephrin (1 c.c. of 1 to 20,000 solution) were administered by inserting the needle of the syringe into the rubber tube immediately above the pinch-cock. After being injected into the tube the drug was quickly and completely washed into the vein with from 6 to 8 c.c. of salt solution. The normal reactions of the animal to standard doses of nicotin and epinephrin were first determined. Known amounts of Witte's peptone in solution, or, in the case of sensitized animals, of normal horse serum, were then injected. After the blood pressure

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* From the Department of Pathology of Northwestern University Medical School.

1. Simonds, J. P.: Jour. Infect. Dis., 1916, xix, 746.
2. Hoskins, Rowley and Rosser: THE ARCHIVES INT. MED., 1916, xvi, 456.
3. Hoskins and Wheelon: Am. Jour. Physiol., 1914, xxxiv, 81.

had reached its lowest level the injections of epinephrin and nicotin were repeated at frequent intervals.

The results are shown graphically in Figures 1 to 4. In Figure 1 sections of the blood pressure tracing of Dog *A*14-*p* are shown. This animal was given 1 c.c. of normal horse serum subcutaneously on Feb. 3, 1915. On February 24 the normal reactions to epinephrin and nicotin were recorded, and 5 c.c. of normal horse serum were injected intravenously. There was no fall in blood pressure during the following twenty minutes and 2 gm. of Witte's peptone in salt solution were given intravenously. The blood pressure fell promptly, but during the period of fall the animal made several violent respiratory efforts, at which time the decline became less steep and even almost ceased for a few seconds. The first injections of nicotin and epinephrin given two and three minutes, respectively, after the administration of the peptone produced no effect either on respiration or blood pressure. (The tracing for epinephrin is not shown.) An injection of nicotin given six minutes after the peptone caused some dyspnea and a rise in pressure greater than the normal for that animal (Fig. 1, 5). One minute later epinephrin caused only a slight rise in pressure (Fig. 1, 6). Two minutes afterward, that is, nine minutes after the injection of the peptone, nicotin gave a markedly exaggerated reaction, the pressure reached almost normal and did not fall again (Fig. 1, 7). It may be noted in passing that the effect of dyspnea in increasing the amplitude of the swing of the manometer is not so evident in these conditions of low blood pressure as when the pressure is at its normal level and the heart filling and emptying itself properly at each beat. This is shown especially well in Figure 4.

Small openings were made between the ribs into the pleural cavities in Dog *P C O* 1 (Fig. 2) and artificial respiration was employed. The normal reactions to epinephrin and nicotin were then recorded. This animal was very sensitive to epinephrin. Two grams of Witte's peptone dissolved in 20 c.c. of salt solution were washed into the femoral vein with 60 c.c. of salt solution. The volume rise was quite marked, but was followed by an immediate fall in blood pressure. During the following thirty minutes none of the frequently repeated injections of nicotin produced anything like the normal response. In most instances the only perceptible result was the slight transient rise that was due to the volume of fluid with which the drug was washed into the vein. The effect of epinephrin, to which this animal was especially sensitive, was evident from the first injection. The last injection of this substance caused a rise in pressure equal to about one-half the normal response for this animal, but it brought the pressure back to approximately its original level, where it remained.

In Dog *P C O* 2 (Fig. 3) the normal reactions to nicotin and

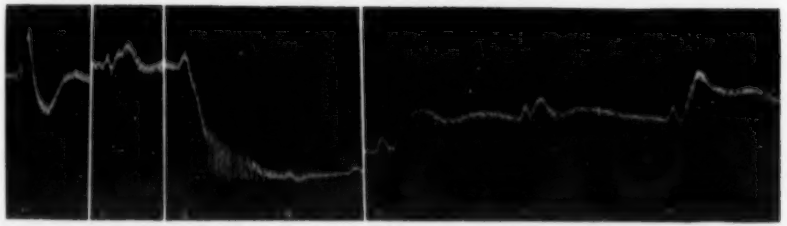

Fig. 1.—Dog A 14p: On February 3, 1 c.c. normal horse serum was injected subcutaneously, and on February 24, 5 c.c. were injected. No fall in blood pressure occurred. Twenty minutes later 2 gm. of Witte's peptone dissolved in salt solution wre given intravenously. Division 1 shows normal reaction to epinephrin; 2 shows normal reaction to nicotin; in 3 there were given 2 gm. of peptone intravenously at 11:22 a. m.; in 4 nicotin was injected at 11:24 a. m., with no reaction. There was no reaction to epinephrin injected one minute later (not shown on tracing). At 5 nicotin was injected (11:28 a. m.). There was dyspnea and an augmented rise in blood pressure, which remained higher than before. At 6 epinephrin was injected (11:29 a. m.). There was decreased reaction to less than one-half the normal. At 7 nicotin was injected (11:31 a. m.). There was dyspnea and exaggerated rise in pressure, which was subsequently sustained at this level.

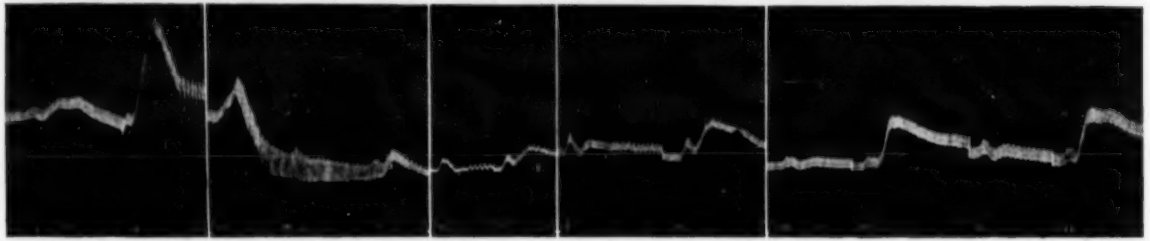

Fig. 2.—Dog P C O 1: To determine the effect of opening the chest and the use of artificial respiration on the reaction to nicotin small openings were made between the ribs into both pleural cavities at 9:35 a. m. At 1 is shown the normal reaction to nicotin with the chest open; at 2 is shown the normal reaction to epinephrin with the chest open. This animal was very sensitive to epinephrin. There were given at 3 Witte's peptone, 2 gm., in salt solution, injected at 9:43 a. m. There was marked volume rise with sharp fall in pressure. At 4 nicotin was injected at 9:44 a. m., and at 5 epinephrin was injected at 9:45 a. m. Again at 6 nicotin was injected with 12 c.c. salt solution at 9:50 a. m.; at 7 epinephrin was injected at 9:52 a. m.; at 8 nicotin was injected at 9:59 a. m.; at 9 epinephrin was injected at 10:01 a. m.; at 10 nicotin was injected at 10:13 a. m.; at 11 epinephrin was injected at 10:15 a. m.; at 12 nicotin was injected at 10:17 a. m.; and at 13 epinephrin was injected at 10:20 a. m.

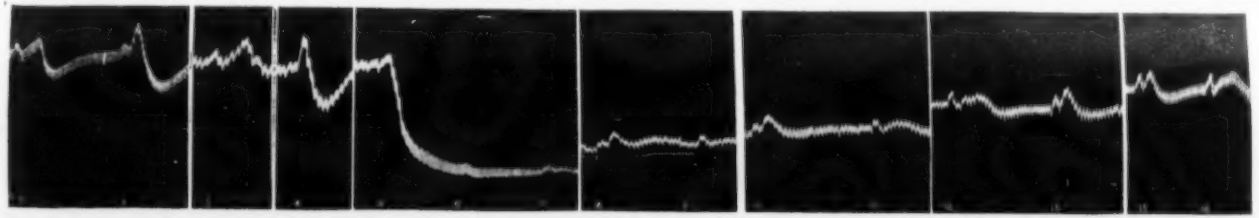

Fig. 3.—Dog P C O 2: This experiment was undertaken to determine the effect of opening the chest on the reaction to nicotin. At 1 is shown the normal reaction to nicotin before opening chest, and at 2 the normal reaction to epinephrin before opening the chest. Small openings made between the ribs into both pleural cavities at 9:35 a. m. At 3 is shown the reaction to nicotin after opening the chest, and at 4 the reaction to epinephrin after opening the chest. At 5 were given 3 gm. Witte's peptone in salt solution at 9:42 a. m. At 6 nicotin was injected at 9:43 a. m.; at 7 epinephrin was injected at 9:44 a. m.; at 8 epinephrin was injected at 9:58 a. m.; at 9 nicotin was injected at 10:04 a. m., with volume rise only. At 10 epinephrin was injected at 10:10 a. m.; at 11 nicotin was injected at 10:12 a. m.; at 12 nicotin was injected at 10:26 a. m., and at 13 epinephrin was injected at 10:27 a. m. The openings in the chest wall were closed with clamps at 10:30 a. m., and the animal breathed spontaneously. At 15 epinephrin was injected at 10:33 a. m., and at 16 nicotin was injected at 10:34 a. m.

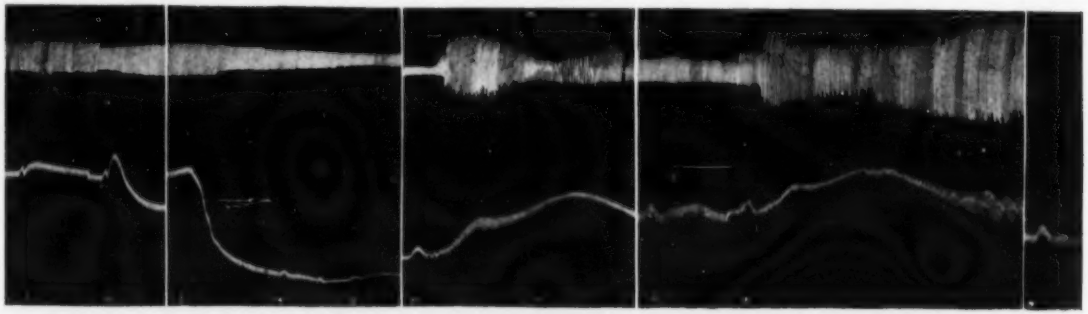

Fig. 4.—Dog P R 1: This experiment shows the effect of violent respiratory effort on blood pressure in peptone shock. The upper tracing shows the respiration, the lower one, blood pressure. (While takin gthis tracing, at a point on the chart between *a* and *b* the rubber tube connecting the tracheal cannula with the Marey tambour became kinked and only a straight line was registered, although the animal was still in a condition of dyspnea. An attempt was made without much success, to trace this in afterward.) At 1 is shown the normal reaction to nicotin, and at 2 the normal reaction to epinephrin. At 3 there were given 2 gm. Witte's peptone in salt solution, injected intravenously, at 10:29 a. m. At 4 nicotin was injected at 10:30 a. m.; at 5 epinephrin was injected at 10:32 a. m.; at 6 nicotin was injected at 11:04 a. m.; at 7 nicotin was injected at 11:30 a. m.; at 8 nicotin was injected at 11:36 a. m., and at 9 nictoin was injected at 11:56 a. m. Five minutes previously the chest had been opened and artificial respiration started.

epinephrin were obtained before (Fig. 3, 1 and 2) and after (Fig. 3, 3 and 4) opening the chest and using artificial respiration. The results show that the process of opening into the pleural cavities and the use of artificial respiration did not materially affect the normal reactions to these drugs. Three grams of Witte's peptone in 30 c.c. of salt solution were then injected intravenously, which caused a prompt and marked fall in blood pressure. The first doses of epinephrin and nicotin caused no perceptible rise. It was only after sixteen minutes had elapsed that epinephrin began to give a reaction (Fig. 3, 8). After twenty-two minutes nicotin still caused no response (Fig. 3, 9). After forty-four and forty-five minutes, respectively, both nicotin and epinephrin gave subnormal reactions, the latter being proportionally stronger than the former. At no time did a standard dose of nicotin cause its normal response.

Figure 4 shows the respiration curve, taken with a Marey tambour, and the blood pressure curve of a dog which was given 2 gm. of Witte's peptone. The effect of dyspnea on the action of nicotin in low blood pressures of this type is well shown. Figure 4, 8 shows the effect of a standard dose of nicotin, given nearly an hour after the onset of shock, which did not, for some reason, affect the respiration. Just why similar doses of nicotin should act on respiration differently at different times in the same animal cannot now be stated. It may have been due to variations in the depth of anesthesia, although there is no particular reason why, in this instance, the degree of anesthesia should have varied greatly. Figure 4, 6 and 8, shows the marked effect of nicotin when dyspnea is produced.

The results of these observations may be stated briefly thus: In conditions of low blood pressure due to anaphylactic shock and peptone poisoning the exaggerated reaction to nicotin frequently observed is associated with violent respiratory effort. Opening the chest and employment of artificial respiration effectively prevent this result, although they do not materially affect the reaction to nicotin before the condition of shock has been induced. It is believed, therefore, that this augmented effect in these two conditions is due to its action on respiration rather than any action on the vasomotor apparatus itself.

Swale Vincent[4] has shown that under conditions of normal blood pressure violent dyspnea has a distinctly depressor effect. Henderson and Barringer[5] believe that "the utmost assistance which respiration can afford to the circulation is to maintain a venous pressure sufficient to distend the right ventricle as rapidly as it relaxes and as fully as the duration of the diastole allows." The "critical venous pressure"

4. Vincent, Swale: Quart. Jour. Physiol., 1915, ix, 45.
5. Henderson and Barringer: Am. Jour. Physiol., 1912-1913, xxxi, 399.

necessary to accomplish this is "not more than 50 mm. of saline."[6] The negative pressure maintained around the heart by the elasticity of the lungs, according to these observers, is approximately equal to the critical venous pressure. Lewis[7] found that in man "a deep intercostal inspiration, which is not prolonged, yields a pure fall in blood pressure; a deep diaphragmatic inspiration, which is not prolonged, gives a pure rise in blood pressure. The rise in blood pressure in abdominal breathing is due to the raised intra-abdominal pressure."

It appears to be generally accepted, therefore, that in the normal animal increased respiration produces little if any rise in blood pressure and may even cause a fall. This is true for several reasons: First, the veins are uniformly filled, venous pressure is normal, and as Henderson and Barringer[6] have pointed out, any suction that might be produced by respiratory effort cannot be transmitted through these collapsible tubes to any distance outside the thorax. Second, with the heart normally filling and emptying itself at each beat, the percentage of blood that could be added by respiratory effort would be small. Third, there is no reservoir of accumulated blood comparatively near the heart on which suction can be exerted.

In anaphylactic and peptone shock, however, an entirely different condition exists. In the first place, the venous pressure is low and the heart is not filling normally. There is room, therefore, for a considerable increase in the percentage of blood that could be added to the heart during each diastole if a source of supply were available. Such a supply is at hand in the overfilled venous trunks and in the veins of the liver and splanchnic area. Even in the process of collapsing under the influence of suction such turgid vessels would deliver to the heart a larger volume of blood than normally filled vessels could do. Furthermore, the veins of the liver are not readily collapsible, and Edmunds[8] has shown that in anaphylactic shock there is a very marked increase in the volume of the liver due to the accumulation of blood in that organ. Suction exerted on the dilated hepatic veins by increased respiratory effort would not cause their collapse, but would draw from them a much greater amount of blood than could thus be extracted from the normal liver. The increased intra-abdominal pressure in dyspnea would help to keep the dilated veins of the liver filled by pressing into them blood from the veins of the splanchnic area.

Low blood pressures due to hemorrhage and to circulatory shock of the type under discussion are, as shown by Henderson,[9] identical

6. Henderson and Barringer: Am. Jour. Physiol., 1912-1913, xxxi, 352.
7. Lewis: Jour. Physiol., 1908, xxxvii, 233.
8. Edmunds: Ztschr. f. Immunitätsforsch. u. exper. Therap., Original, 1914, xxii, 181.
9. Henderson: Am. Jour. Physiol., 1910, xxvii, 152.

in mechanism, in that in both the venous supply to the right side of the heart is the critical factor. In both the venous pressure is low and too little blood reaches the right side of the heart. But there is this sharp difference, that in the circulatory shock there is a large reservoir of stagnant blood in the veins of the liver and splanchnic region, while after hemorrhage no such reservoir is present. This distinction is important from a therapeutic standpoint and in the interpretation of the results of the injection of nicotin reported above.

In low blood pressure from hemorrhage, as shown by Hoskins, Rowley and Rosser[10] there is an increased irritability of the vasomotor center as manifested by the augmented reaction to nicotin. This phenomenon, in this case, is undoubtedly chiefly if not wholly of central origin. The mechanical effect of increased respiratory effort under such conditions would be slight because of the absence of any reservoir of accumulated blood on which suction could be exerted; and because the veins, being already underfilled, would collapse all the more readily and suction could not be transmitted through them even to the slight extent to which it is transmitted through normal veins.

In the case of low blood pressure from anaphylactic and peptone shock, however, an entirely different condition exists. In the first place, the greatly reduced response to injections of nicotin that are observed when, for any reason, dyspnea is not produced, is suggestive of a condition of reduced irritability of the vasomotor center (Fig. 4, 7). When, however, dyspnea is produced, suction is exerted on the overfilled veins of the liver and sufficient blood is drawn into the heart to cause an exaggerated rise in pressure.

In human patients in the treatment of shock associated with low blood pressure not due to hemorrhage, Pearce and Eisenbrey[11] recommend the use of epinephrin and intravenous injections of salt solutions. Neither of these procedures was effective in my animals, although it is quite possible that they might be more so in human cases. In my animals the paralysis of the nerve endings in the vessel walls was too great for the epinephrin to cause a rise in pressure. Intravenous injections of comparatively large quantities of salt solution yielded relatively slight increase in pressure. The added fluid apparently went chiefly to increase the dilatation of the splanchnic vessels. For example, a dog in peptone shock with a blood pressure of 32 mm. of mercury received, during a period of two minutes, 225 c.c. of salt solution at 40 C. As a result of this treatment, the highest pressure reached was 48 mm. of mercury, and by the end of three minutes

10. Hoskins, Rowley and Rosser: THE ARCHIVES INT. MED., 1915, xvi, 456.
11. Pearce and Eisenbrey: THE ARCHIVES INT. MED., 1910, vi, 218.

from the beginning of the injection, the pressure had sunk to 40 mm., above which it did not again rise, and the animal ultimately succumbed.

In such cases the injection of nicotin, on the other hand, by causing increased respiratory effort, led to rise in blood pressure and frequently saved the life of the animal, even when death seemed imminent.[12] In the treatment of this type of circulatory shock in man it is possible that any measure which will excite more or less dyspnea (not necessarily nicotin) would raise blood pressure and improve the condition of the patient. Perhaps, when possible, voluntary deep and rapid breathing on the part of the patient at frequent intervals might work good results. It might at least help to prevent a serious loss of tonus from a too long-continued overdistention of the vessels concerned.

SUMMARY

The condition of low blood pressure due to anaphylactic shock and peptone poisoning is characterized by absen e or marked diminution of the reaction to epinephrin, and an exaggerated response to nicotin. It would appear that there is a condition of reduced irritability on the part of the vasomotor center, and that the increased reaction to nicotin is largely mechanical, resulting from the effect of the drug on respiration. The dyspnea so produced causes suction on the overfilled noncollapsible veins of the liver and brings sufficient blood to the underfilled right side of the heart and ultimately to the systemic vessels, in which the pressure is raised. It is suggested that in cases of shock in man, associated with low blood pressure not due to hemorrhage, the artificial production of dyspnea or the voluntary increase of the rate and depth of respiration by the patient may lead to improvement.

12. Simonds, J. P.: Footnote 1, Chart 2.

CONTENTS OF VOLUME XVIII

OCTOBER, 1916. NUMBER 4.

PAGE

RENAL FUNCTION IN PERNICIOUS ANEMIA AS DETERMINED BY DIETARY RENAL TESTS. HENRY A. CHRISTIAN, M.D., BOSTON 429

AUTOGENOUS DEFIBRINATED BLOOD IN THE TREATMENT OF BRONCHIAL ASTHMA. MORRIS H. KAHN, M.D., AND H. W. EMSHEIMER, M.D., NEW YORK 445

THE ALBUMIN AND GLOBULIN CONTENT OF HUMAN BLOOD SERUM IN HEALTH, SYPHILIS, PNEUMONIA, AND CERTAIN OTHER INFECTIONS, WITH THE BEARING OF GLOBULIN ON THE WASSERMANN REACTION. ALBERT H. ROWE, M.D., OAKLAND, CALIF. 455

THE BLOOD PLATELETS IN HEMOPHILIA. GEORGE R. MINOT, M.D., AND ROGER I. LEE, M.D., BOSTON 474

THE EXCRETION OF CHLORIDS AND WATER AND THE RENAL FUNCTION IN SERUM DISEASE. FRANCIS M. RACKEMANN, M.D., WARFIELD T. LONGCOPE, M.D., AND JOHN P. PETERS, M.D. 496

INFLUENCE OF AGE AND SEX ON HEMOGLOBIN. A SPECTROPHOTOMETRIC ANALYSIS OF NINE HUNDRED AND NINETEEN CASES. CHARLES SPENCER WILLIAMSON, M.D., CHICAGO 505

THE AUTOLYSIS OF NITROGENOUS COMPOUNDS OF THE BLOOD SERUM IN GENERAL PARALYSIS AND DEMENTIA PRAECOX, WITH ITS BEARING ON THE ABDERHALDEN TEST. H. DOUGLAS SINGER, M.D., AND W. R. QUANTZ, PH.D., HOSPITAL, ILL. 529

AMMONIUM SALTS AND THE ABDERHALDEN TEST. H. DOUGLAS SINGER, M.D., AND WILLIAM R. QUANTZ, M.D., HOSPITAL, ILL. 538

HEMATOCHYLURIA; OBSERVATIONS ON THE FAT CONTENT OF THE URINE AND THE PATHOLOGY OF THE CONDITION. D. W. CARTER, JR., M.D., BOSTON 541

METABOLISM STUDIES OF ANGIONEUROTIC EDEMA. T. GRIER MILLER, M.D., AND O. H. PERRY PEPPER, M.D., PHILADELPHIA 557

NOVEMBER, 1916. NUMBER 5

PAGE

THE ACTION OF THE SO-CALLED FEMALE REMEDIES ON THE EXCISED UTERUS OF THE GUINEA PIG. J. D. PULCHER, M.D., G. E. BURMAN AND W. R. DELZELL, OMAHA 557

GLUCOSE FORMATION FROM PROTEIN IN DIABETES. N. W. JANNEY, M.D., NEW YORK 584

SOME STUDIES OF A DIURETIC (THEOCIN). HENRY A. CHRISTIAN, M.D., BOSTON 606

THE TOXIC EFFECTS OF UREA ON NORMAL INDIVIDUALS. A. W. HEWLETT, M.D., Q. O. GILBERT, M.D., AND A. D. WICKETT, M.D., ANN ARBOR, MICH. 636

THE RELATION OF RECURRENT ATTACKS OF PELLAGRA TO RACE, SEX AND AGE OF THE PATIENT AND TO TREATMENT OF THE DISEASE. J. F. SILER, M.D., P. E. GARRISON, M.D., AND W. J. MACNEAL, M.D., NEW YORK 652

EXPERIMENTAL STUDY OF THE MONONUCLEAR CELLS OF THE BLOOD AND TISSUES. WITH SPECIAL REFERENCE TO THE SO-CALLED TRANSITIONAL CELL. FRANK A. EVANS, M.D., NEW YORK 692

PHOSPHATE RETENTION AS A FACTOR IN THE PRODUCTION OF ACIDOSIS IN NEPHRITIS. W. MCKIM MARRIOTT, M.D., AND JOHN HOWLAND, M.D., BALTIMORE 708

VENTRICULAR RESPONSE TO AURICULAR PREMATURE BEATS AND TO AURICULAR FLUTTER. PAUL D. WHITE, M.D., AND HAROLD W. STEVENS, M.D., BOSTON 712

CONTENTS

PAGE

ACIDOSIS IN ACUTE AND CHRONIC DISEASE. CHANNING FROTHINGHAM, JR., M.D., BOSTON 717

SENSORY DISTURBANCES OF CEREBRAL ORIGIN. CONSIDERATION OF TYPES AND OF DIAGNOSTIC ELEMENTS. ALFRED GORDON, M.D., PHILADELPHIA 733

THE ACTION OF THE VARIOUS FEMALE REMEDIES ON THE EXCISED INTESTINE OF THE RABBIT. W. K. DELZELL, G. E. BURMAN AND J. D. PILCHER, M.D., OMAHA 752

A STUDY OF A CASE OF INTERMITTENT COMPLETE DISSOCIATION OF AURICLES AND VENTRICLES PRESENTING UNUSUAL FEATURES. JAMES D. HEARD, M.D., AND A. H. COLWELL, M.D., PITTSBURGH 758

EXPERIMENTS ON THE ORIGIN AND CONDUCTION OF THE CARDIAC IMPULSE. VI. CONDUCTION OF THE EXCITATION FROM THE SINO-AURICULAR NODE TO THE RIGHT AURICLE AND AURICULOVENTRICULAR NODE. J. A. E. EYSTER, M.D., AND WALTER J. MEEK, PH.D. 775

A METABOLISM STUDY OF GOITER, WITH THE EFFECT OF THYROID AND THYMUS TREATMENT. JOHN O. HALVERSON, PH.D., OLAF BERGEIM, PH.D., AND PHILIP B. HAWK, PH.D., PHILADELPHIA 800

THE RELATION OF CHANGES IN THE FORM OF THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM TO FUNCTIONAL CHANGES IN THE HEART. G. CANBY ROBINSON, M.D., ST. LOUIS 830

A STUDY OF LOW BLOOD PRESSURES NOT ASSOCIATED WITH TRAUMA OR HEMORRHAGE. J. P. SIMONDS, M.D., CHICAGO 848

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